Single Technology Appraisal

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis [ID6446]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis [ID6446]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Boehringer Ingelheim
2. **Company Addendum**
3. **Company summary of information for patients (SIP)** from Boehringer Ingelheim
4. **Clarification questions and company responses**
5. **Patient group, professional group and NHS organisation submissions** from:
   a. Action for Pulmonary Fibrosis (APF)
   b. Association of Respiratory Nurses
6. **Expert personal perspectives** from:
   a. Dr Sophie Fletcher, Consultant in Respiratory Medicine – clinical expert, nominated by Action for Pulmonary Fibrosis
   b. Professor Philip Molyneaux, Professor of Interstitial Lung Disease – Clinical expert, nominated by Boehringer Ingelheim
   c. Mr Bradley Price – Patient Expert nominated by Action for Pulmonary Fibrosis
7. **External Assessment Report** prepared by Aberdeen HTA Group
8. **External Assessment Report – factual accuracy check**
9. **Clinical Experts Response to additional questions**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis [ID6446]

Company evidence submission

February 2026

File name	Version	Contains confidential information	Date
ID6446 Nerandomilast company evidence submission	**1.0**	**Yes**	**20 February 2026**

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Abbreviations

Abbreviation	Definition
3L	Third-line
AE	Adverse event
AESI	Adverse event of special interest
AF	Antifibrotic
APF	Action for Pulmonary Fibrosis
bid	Twice a day
BSC	Best supportive care
CI	Confidence interval
CPI	Composite Physiologic Index
CTCAE	Common Terminology Criteria for Adverse Events
DBL1	Database lock 1
DBL2	Database lock 2
EAG	Evidence Assessment Group
DILI	Drug-induced liver injury
DL_{CO}	Diffusing capacity of the lungs for carbon monoxide
FAS	Full analysis set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GAP	Gender, Age, Physiology
HCRU	Healthcare resource use
HR	Hazard ratio
HRCT	High-resolution computed tomography
HRQL	Health-related quality of life
ILD	Interstitial lung disease
IPD	Individual patient-level data
IPF	Idiopathic pulmonary fibrosis
IPTW	Inverse probability of treatment weighting
ITC	Indirect treatment comparison
L-PF	Living with Pulmonary Fibrosis questionnaire
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NMA	Network meta-analysis
OR	Odds ratio
PDE4B	Phosphodiesterase 4B
OS	Overall survival

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Abbreviation	Definition
PF-ILD	Progressive fibrosing interstitial lung disease
PPF	Progressive pulmonary fibrosis
PT	Preferred term
RCT	Randomised controlled trial
RWD	Real-world data
RWE	Real-world evidence
SARD-ILD	Systemic-autoimmune-rheumatic disease interstitial lung disease
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TAs	Technology appraisals
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TS	Treated Set
TSD	Technical support document
TTD	Time to treatment discontinuation
UIP	Usual interstitial pneumonia

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1 Decision problem, description of the technology and clinical care pathway

- Idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF) are progressive fibrosing forms of interstitial lung disease (ILD)[1, 2]
- Approximately 7,000 new cases of IPF and PPF are diagnosed each year with estimated incidence of 10 per 100,000 for IPF and 1.5 per 100,000 for PPF[3, 4]
- IPF and PPF result from chronic and uncontrolled inflammation and fibrosis in response to lung injury that causes irreversible scarring of the lungs, referred to as pulmonary fibrosis[5-7]
- Pulmonary fibrosis stiffens the lungs and limits their ability to function, and thus is associated with high morbidity and early mortality[5-7]
- The most common symptoms of pulmonary fibrosis are breathlessness, persistent cough and fatigue that markedly impact patient mobility and ability to complete basic tasks of day-to-day living[8-10]
- Patients may ultimately become dependent on oxygen to help them breathe which further limits day-to-day living and poses an out-of-pocket expense[11]
- Survival outcomes remain worse than in several common cancers with a 5-year survival rate post-diagnosis of only 45%[9] despite the introduction of current antifibrotic (AF) therapies, nintedanib and pirfenidone, over a decade ago
- The high morbidity and early mortality impact of IPF and PPF negatively affect the health-related quality of life (HRQL) of patients and their carers, with high rates of anxiety, depression, stress and other mental health impacts reported[8, 12]
- In a recent survey of people living with pulmonary fibrosis in the UK, many said they would prefer to have a cancer diagnosis, citing the stark prognosis associated with a diagnosis of pulmonary fibrosis and lack of support[9]
- Therapies can slow the rate of disease progression but are associated with safety and tolerability concerns that frequently lead to dose reductions and treatment discontinuations and mean they are not suitable for all people with pulmonary fibrosis[13-20]

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- People living with IPF and PPF have a clear and urgent unmet need for an effective, safe and well tolerated new treatment option that can slow disease progression, improve life expectancy, and preserve their HRQL

1.1 Decision problem

The submission focuses on nerandomilast as a monotherapy for the treatment of idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF), rather than as an add-on or combination treatment with current antifibrotic (AF) therapy. This reflects the intended use of nerandomilast in clinical practice, aligning to where it provides the most clinical benefit and optimal cost-effectiveness.

Further details are provided in the decision problem summary presented in Table 1.

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Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis	People with IPF or PPF	No difference.
Intervention	Nerandomilast	Nerandomilast monotherapy (18 mg bid)	Focused to the intended use (monotherapy) and recommended dosing of nerandomilast (18 mg bid, in line with expected marketing authorisation). Results for nerandomilast monotherapy at the lower dose of 9 mg bid are also shown for reference in clinical data tables and figures, as this dose will be available for patients unable to tolerate the 18 mg bid dosing.
Comparator(s)	Established clinical management without nerandomilast, including but not limited to: For idiopathic pulmonary fibrosis: • nintedanib • pirfenidone (in people who have a FVC of 50% to 80% predicted) • best supportive care For progressive pulmonary fibrosis: • nintedanib	For IPF: • nintedanib • pirfenidone (in people who have a FVC of 50% to 80% predicted) • best supportive care For PPF: • nintedanib • best supportive care	For PPF: Immunosuppressants, corticosteroids, infliximab and rituximab may be used to treat the underlying ILD but are not licensed for the treatment of PPF in the UK. Nintedanib is currently the only licensed treatment for PPF in the UK. Immunosuppressants, corticosteroids, infliximab and rituximab may be used alongside nintedanib in the current pathway of care and could also be used in this concomitant way with nerandomilast. Nerandomilast would not replace these treatments and, as such, they do not meet

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• immunosuppressants, such as methotrexate, azathioprine, cyclophosphamide or mycophenolate • corticosteroids • infliximab • rituximab • best supportive care		the definition of a comparator as per the NICE process and methods.
Outcomes	The outcome measures to be considered include: • pulmonary function • physical function • exacerbation rate • hospitalisations • lung transplantation • mortality • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • pulmonary function • physical function • exacerbation rate • hospitalisations • mortality • adverse effects of treatment • health-related quality of life	While lung transplantation could be considered a marker for progression of lung disease, it is not a relevant outcome for this patient population. Patients whose pulmonary function declines to FVC <50% predicted may be considered for lung transplantation, but internal estimates and the FIBRONEER trial programme suggest that a small proportion of patients with IPF or PPF ultimately undergo lung transplantation – around [redacted]%.[21, 22] This is supported by <5% lung transplantation referral rates captured in the BTS ILD Registry.[23]
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Idiopathic pulmonary fibrosis • Progressive pulmonary fibrosis	• IPF • PPF	No difference from the final NICE scope. Data for IPF and PPF are presented separately in Section 2.6 aligning to the FIBRONEER trial programme.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Disease severity defined by FVC		Post hoc pooled IPF and PPF analyses are presented in Section 2.9. Pre-specified subgroup analyses based on baseline FVC % predicted ≤ and >70% for the FAS population are presented in Appendix C. Post-hoc subgroup analyses based on baseline FVC % predicted ≤ and >80% for the monotherapy population are under investigation.
Key: bid, twice a day; BTS British Thoracic Society; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NICE, National Institute for Health and Care Excellence; PPF, progressive pulmonary fibrosis.			

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1.2 Description of the technology being evaluated

A description of nerandomilast is presented in Table 2. The draft Summary of Product Characteristics (SmPC) for nerandomilast is provided in Appendix A. The UK Public Assessment Report for this indication can be provided on availability.

Nerandomilast is the first preferential inhibitor of phosphodiesterase 4B (PDE4B) with AF and immunomodulatory properties for people with IPF and PPF. PDE4B is an isoenzyme that is highly expressed in the lungs and immune cells, where it plays an important role in fibrosis and inflammation (Table 2).[24-26]

Based on promising preclinical and early-phase clinical trial data, nerandomilast was granted Breakthrough Therapy Designation for the treatment of IPF by the US Food and Drug Administration (FDA), accelerating its clinical development.[27] Nerandomilast is now licensed in the US for IPF and PPF and is under regulatory review in the UK and Europe for IPF and PPF, with regulatory files submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) in [redacted] and approval expected in [redacted]

Table 2: Technology being evaluated

UK approved name and brand name	Nerandomilast (Jascayd®)
Mechanism of action	Nerandomilast (BI 1015550) is an oral inhibitor of PDE4 with preferential inhibition of the PDE4B isoenzyme, which is highly expressed in the lung and plays an important role in fibrosis and inflammation in the lungs.[25, 28] Nerandomilast has the potential to reduce microvascular permeability and improve endothelial function. More specifically, PDE4B inhibition in the lung is expected to inhibit profibrotic growth factors and inflammatory cytokines, which are overexpressed in IPF and PPF; to decrease fibroblast proliferation, transformation of fibroblast to myofibroblast, and fibroblast motility; as well as to promote cell death of fibroblasts and to decrease synthesis, release, and function of ECM components.[24] Nerandomilast shows ~10 fold selectivity for the PDE4B isoenzyme over PDE4A, PDE4C and most importantly PDE4D, which has been most strongly linked with the gastrointestinal side effects of currently marketed PDE4 inhibitors in other therapy areas.[24]

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Marketing authorisation status	Nerandomilast has been submitted for regulatory review by the MHRA via the national procedure in [redacted]. The anticipated date of regulatory approval from the MHRA is [redacted]
Indications and any restriction(s) as described in the Summary of Product Characteristics (SmPC)	• Nerandomilast is indicated for the treatment of adult patients with IPF • Nerandomilast is indicated for the treatment of adult patients with PPF
Method of administration and dosage	• The recommended dosage is 18 mg bid, administered orally approximately 12 hours apart • Based on individual patient tolerability, the dosage may be reduced to 9 mg bid • If patients are receiving concomitant strong CYP3A inhibitors, the dosage must be reduced to 9 mg bid
Additional tests or investigations	No additional tests or investigations are needed beyond those used to diagnose and treat IPF and PPF in current clinical practice.
List price and average cost of a course of treatment	£3,825 per 60 * 18 mg tablets
Patient access scheme (if applicable)	A proposed patient access scheme: £[redacted] per 60 * 18 mg tablets

Key: bid, twice a day; CYP3A, Cytochrome P450, family 3, subfamily A; ECM, extracellular matrix; IFU, information for use; IPF, idiopathic pulmonary fibrosis; MHRA, Medicines and Healthcare products Regulatory Agency; PPF, progressive pulmonary fibrosis.
Source: Nerandomilast SmPC, 2025.[29]

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1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Disease overview

IPF and PPF are chronic, progressive forms of interstitial lung disease (ILD) characterised by an irreversible decline in lung function associated with high morbidity and early mortality, despite current standard of care.[1, 2, 9] Pathogenesis of IPF and PPF is driven by an abnormal response to lung injury. Injury to the lung tissue induces various inflammatory and fibrotic responses to repair the damaged tissue.[6, 7] In IPF and PPF, these responses become unregulated, leading to chronic and uncontrolled inflammation and fibrosis, and resulting in an irreversible scarring of the lungs that makes them stiff and limits their ability to function properly.[5-7] This irreversible scarring of the lungs in response to lung tissue injury is referred to as pulmonary fibrosis.[9]

Historically, the term progressive fibrosing interstitial lung disease (PF-ILD) has been used as an alternative term for PPF in the clinical community[30]; data and evidence referring to PF-ILD are thus representative of PPF. In the NICE scope, PF-ILD is used as a collective term for IPF and PPF. To avoid any confusion from hereon in, the term pulmonary fibrosis will be used as a collective term for IPF and PPF and the terms IPF and PPF will be used for the individual conditions.

1.3.1.1 Aetiology

IPF is a progressive fibrosing form of ILD of unknown aetiology, whereas PPF is a progressive clinical phenotype observed in people with ILD of known or unknown aetiology, other than IPF.[30-32] PPF can therefore be diagnosed in people with different underlying ILD diagnoses, including systemic-autoimmune-rheumatic disease (SARD)-ILDs such as rheumatoid arthritis-, systemic sclerosis- and sarcoidosis-associated ILD and non-SARD ILDs such as exposure-related ILD, as summarised in Figure 1. While both conditions involve unregulated responses to lung injury and chronic fibrosis, inflammation may play a more prominent role in PPF, depending on the underlying cause.[6, 33, 34]

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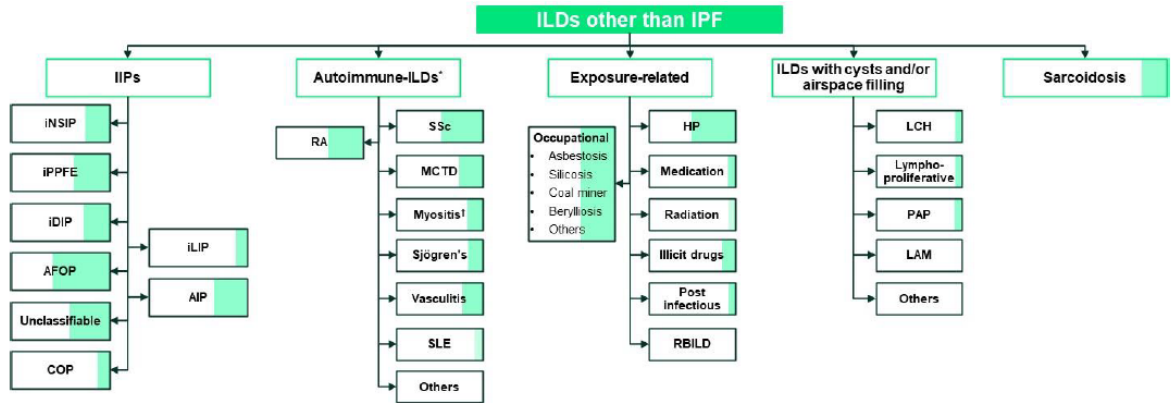
Figure 1: Estimated proportion of ILDs other than IPF that may manifest PPF (green shading)



Key: ACR/CHEST, American College of Rheumatology/American College of Chest Physicians; AFOP, acute fibrinous and organising pneumonia; AIP, acute interstitial pneumonia; COP, cryptogenic organising pneumonia; HP, hypersensitivity pneumonitis; iDIP, idiopathic DIP; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; iLIP, idiopathic lymphoid interstitial pneumonia; iNSIP, idiopathic non-specific interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; iPPFE, idiopathic pleuroparenchymal fibroelastosis; LAM, lymphangioleiomyomatosis; LCH, Langerhan's cell histiocytosis; MCTD, mixed connective tissue disease; PAP, pulmonary alveolar proteinosis; PPF, progressive pulmonary fibrosis; RA, rheumatoid arthritis; RBILD, Respiratory Bronchiolitis-Associated ILD; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.
Notes: The green shaded areas represent the estimated proportion of patients with various types of ILD who manifest PPF. Note that IPF is not included in the figure because it is excluded from the definition of PPF. While virtually all patients with IPF will manifest disease progression similar to PPF, the proportion of patients with ILDs other than IPF who manifest PPF is based on the consensus of opinions and the perception of the international committee. There are no data to provide the exact proportion of patients manifesting PPF in ILDs, other than IPF. *Systemic-autoimmune-rheumatic disease-associated ILDs and †idiopathic inflammatory myositis in the ACR/CHEST 2023 guidelines (Johnson et al. [2024]).
Source: Raghu et al., 2022.[30]

1.3.1.2 Patient numbers, demographics and risk factors

Approximately 7,000 new cases of IPF and PPF are diagnosed each year, with estimated incidence of 10 per 100,000 for IPF and 1.5 per 100,000 for PPF.[3, 4] Around 30,000 to 40,000 people are already living with IPF in England and Wales based on estimated prevalence of 50 to 60 per 100,000.[4, 35] Estimating the number of people already living with PPF is more difficult as data are normally only captured for the underlying ILD diagnoses[35]. A retrospective observational study conducted across nine tertiary ILD centres in England identified 253 new cases of PPF in 1,749 people living with non-IPF ILD over a 6-month period (August 2017–January 2018), despite standard therapy; this translates to 15% of people living with non-IPF ILD developing PPF.[2]

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IPF predominantly affects older adults, with a mean age range of [redacted]74 years in the UK[36, 37] and there are a higher proportion of males affected with > 60% of people living with IPF being male.[38-42] Although the aetiology of IPF remains unknown, several risk factors have been identified, including genetics, smoking, environmental exposures and viral or bacterial infections.[38-43]

The demographic profile of PPF varies depending on the underlying ILD diagnosis.[44] The mean age range of people living with PPF is [redacted]68 years in the UK, but it can affect people of younger working age.[2, 36] In contrast to IPF, on average, there are a slightly higher proportion of females affected, with > 50% of people living with PPF being female.[2, 36] However, like other demographics gender is heavily dependent on the underlying ILD diagnosis with female predominance observed in SARD ILDs and male predominance observed in non-SARD ILDs.[2, 36] Risk factors for PPF include familial pulmonary fibrosis, smoking, environmental exposures and other specific risk factors to the underlying ILD diagnosis.[44]

1.3.1.3 Disease course and prognosis

Both IPF and PPF are characterised by a heterogeneous and unpredictable disease course. However, while individual trajectories vary, nearly all patients experience progressive decline over time, leading to worsening physical and pulmonary function, increased healthcare needs and premature mortality. Survival outcomes remain poor, and are worse than in several common cancers, highlighting the severity and life-limiting nature of the condition.[9]

Median survival following diagnosis of IPF is approximately 3.5–5 years with a 5-year survival rate of only 45%.[1, 9] Over 5,000 people die from IPF in the UK every year, with IPF responsible for 1% of all UK deaths.[35, 45] In a retrospective analyses of data collected at ILD specialist centres in the UK, survival of people with PPF was shown to be no different to people with IPF (hazard ratio [HR]: 1.06; 95% confidence interval [CI]: 0.84, 1.35; p = 0.6).[2] This study also showed that people with a progressive clinical phenotype (PPF) had significantly higher mortality than people living with non-progressive ILD (HR: 3.32; 95% CI: 2.53, 4.37; p < 0.001) despite standard therapy in both groups.[2] Findings from post hoc analyses of the nintedanib trial programme[46] further show the similarity in disease courses across IPF and PPF,

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with data from this post hoc analyses leading NICE to previously conclude that it is reasonable to consider that these conditions share similar disease trajectories.[47]

Pulmonary function, as measured by forced vital capacity (FVC) and/or diffusing capacity of the lungs for carbon monoxide (DL_{CO}), is a consistent and clinically relevant marker of the disease course in pulmonary fibrosis.[48, 49] Declines in FVC and DL_{CO} are representative of worsening prognosis. In particular, a relative decline in FVC of at least 10% predicted is commonly accepted to define progression and is associated with increased disease morbidity and mortality.[18, 47, 50, 51] However, the relationship between FVC and DL_{CO} decline to mortality is not linear, which limits the reliability of these parameters as surrogate endpoints for survival.[48, 49, 52-54]

Acute exacerbations, defined as sudden and severe worsening of respiratory symptoms, occur in some patients and can further complicate the disease course.[49] In IPF, acute exacerbation events have been reported to occur in up to 25% of patients within 3 years of diagnosis.[55, 56] However, defining acute exacerbations remains challenging due to complex and variable diagnostic criteria, which often result in poor reproducibility and misclassification.[57] Many reported events fail to meet strict criteria upon adjudication, creating uncertainty in epidemiological estimates and comparability of clinical evidence. Additional difficulties include distinguishing acute exacerbations from acute lung injury caused by infection or cardiogenic pulmonary oedema. Accurate diagnosis typically requires invasive microbiological testing, which is often impractical and poses considerable risk to patients.[57] Nonetheless, acute exacerbations are accepted to be associated with worsening prognosis, with such events estimated to nearly double the risk of mortality in IPF (multivariate hazard risk = 1.868, $p < 0.001$).[57, 58] Similarly, in PPF, acute exacerbations are linked to accelerated disease progression and increased mortality risk.[59]

1.3.2 Diagnosis

ILDs, including IPF and PPF, are officially diagnosed, assessed for treatment, and managed from ILD specialist centres in the UK. A report from the Interstitial Lung Disease Interdisciplinary Network documented 10,358 patient referrals to ILD specialists in 2022 (patient cases of IPF/PPF not provided separately).[60]

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Diagnosis is complex and requires a multidisciplinary team, with care typically coordinated by ILD/respiratory specialists and in some cases rheumatologists (i.e. if the patient has underlying SARD-ILD). Clinical features, physiological features and radiological features based on high-resolution computed tomography (HRCT) are considered.

Accurate diagnosis of IPF and subsequent diagnostic intervention is based on four diagnostic classifications of usual interstitial pneumonia (UIP) as shown in Figure 2.[30] If confident diagnosis cannot be made based on clinical, physiological and radiological features, histopathology is also considered.

Figure 2: IPF diagnosis on the basis of HRCT and biopsy patterns

IPF suspected*		Histopathology pattern†			
		UIP	Probable UIP	Indeterminate for UIP or biopsy not performed	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)‡	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)‡	Indeterminate§	Non-IPF dx
	Alternative diagnosis	IPF (Likely)‡	Indeterminate§	Non-IPF dx	Non-IPF dx

Key: BAL, bronchoalveolar lavage; CT, computed tomography; dx, diagnosis; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.
Notes: * "Clinically suspected of having IPF" is defined as unexplained patterns of bilateral pulmonary fibrosis on chest radiography or chest CT, bibasilar inspiratory crackles, and age > 60 years. Middle-aged adults (aged > 40 and < 60 years) can rarely present with otherwise similar clinical features, especially in patients with features suggesting familial pulmonary fibrosis. † Diagnostic confidence may need to be downgraded if histopathological assessment is based on transbronchial lung cryobiopsy given the smaller biopsy size and greater potential for sampling error compared with surgical lung biopsy. ‡ IPF is the likely diagnosis when any of the following features are present: 1) moderate-to-severe traction bronchiectasis and/or bronchiolectasis (defined as mild traction bronchiectasis and/or bronchiolectasis in four or more lobes, including the lingula as a lobe, or moderate-to-severe traction bronchiectasis in two or more lobes) in a man aged > 50 years or in a woman aged > 60 years; 2) extensive (> 30%) reticulation on HRCT and age > 70 years; 3) increased neutrophils and/or absence of lymphocytosis in BAL fluid; and 4) multidisciplinary discussion produces a confident diagnosis of IPF. § Indeterminate for IPF 1) without an adequate biopsy remains indeterminate and 2) with an adequate biopsy may be reclassified to a more specific diagnosis after multidisciplinary discussion and/or additional consultation.
Source: Raghu et al., 2022.[30]

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As a clinical phenotype, PPF is defined in patients with ILD of known or unknown aetiology, other than IPF, with radiological evidence of pulmonary fibrosis when at least two of the following three criteria occur within the past year with no alternative explanation: worsening respiratory symptoms, physiological evidence of disease progression and/or radiological evidence of disease progression.[30] This definition is set out in the official American Thoracic Society, European and Japanese Respiratory Societies and the Latin America Thoracic Association Clinical Practice Guideline, and detailed further in Table 3. It is important to note that currently, no specific code in the International Classification of Diseases, Tenth Revision (ICD-10), the Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT), or the Read code system is assigned for the diagnosis of PPF, other than codes for the underlying ILD. This absence of a distinct coding category makes it more challenging to identify patients with PPF in medical records, hindering both clinical management and research.

Table 3: Definition of progressive pulmonary fibrosis

In patients with ILD of known or unknown aetiology, other than IPF, who have radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation:
1. Worsening respiratory symptoms
2. Physiological evidence of disease progression (either of the following): a) Absolute decline in FVC ≥ 5% predicted within 1 year of follow-up b) Absolute decline in DL_{CO} (corrected for haemoglobin) of ≥ 10% predicted within 1 year of follow-up
3. Radiological evidence of disease progression (one or more of the following): a) Increased extent or severity of traction bronchiectasis and bronchiolectasis b) New ground-glass opacity with traction bronchiectasis c) New fine reticulation d) Increased extent of increased coarseness of reticular abnormality e) New or increased honeycombing f) Increased lobar volume loss
Key: DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis. **Source:** Raghu et al. 2022.[30]

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1.3.2.1 Severity assessment

The severity of IPF and PPF is commonly classified using measures of pulmonary function, most commonly FVC % predicted where thresholds are used to define mild, moderate and severe disease (thresholds not presented as they are subjective).[61] The FVC % predicted helps inform treatment decisions in clinical practice (see Section 1.3.4), with the following thresholds used to determine treatment options in the UK: <50% versus 50-80% versus >80% FVC predicted.[62] Additional tools include: the Composite Physiologic Index (CPI), which integrates FVC, DL_{CO} and forced expiratory volume in 1 second (FEV_1) to provide a CPI score with higher scores representing more severe disease[63]; and the Gender, Age, Physiology (GAP) index, which stratifies patients into Stages I–III with corresponding 1-year mortality risks of 6%, 16% and 39%.[63] However, the CPI and GAP scores are not always recorded or considered for treatment decisions in clinical practice.

1.3.2.2 Challenges in diagnosis

Diagnosis of pulmonary fibrosis is frequently delayed, largely due to the non-specific nature of early symptoms, such as breathlessness, coughing and fatigue (see Section 1.3.3.1), which are commonly misattributed to more prevalent respiratory and non-respiratory conditions.[64] According to a large UK survey conducted by the Action for Pulmonary Fibrosis (APF) charity in 2023, more than one-third of patients experience initial misdiagnosis, commonly as asthma, pneumonia, or cardiac or gastrointestinal conditions, resulting in delayed specialist referral and optimal management.[65] As well as the non-specific nature of symptoms, the absence of a specific disease label and the progressive nature of the symptoms in PPF further inputs to diagnostic delay.[2, 60] In practice, this delay is compounded by the lack of formal pathways for patients and insufficient multidisciplinary ILD workforce such as dedicated ILD pharmacists, senior nurses and radiologists that would help to implement diagnostic procedures, i.e. pulmonary function testing and HRCTs and treatment.[60] Data from the British Thoracic Society ILD registry (2024) showed that across ILD specialist centres in the UK, the mean time from referral to presentation was 132 days, with 38% of patients experiencing symptoms for more than 2 years before their first visit to an ILD clinic.[37] This is more than double the recommended time to referral, with the National Health Service (NHS) England ILD Quality

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Dashboard recommending that patients be seen in a clinic within 54 days of referral due to the 'cancer-like' outcomes of IPF.[37] Data from a PPF-ILD Disease Specific Programme in the UK (2024) report that people with IPF experienced a [redacted] delay from symptom onset to diagnosis on average, while people with PPF experienced a [redacted] delay to ILD diagnosis, followed by another [redacted] before PPF confirmation.[36] Within this considerable diagnostic period, pulmonary fibrosis continues to progress without adequate treatment.

Many patients with pulmonary fibrosis report feeling underserved by the healthcare system, citing limited access to basic assessments and delays in diagnosis, and in some cases express a preference for a cancer diagnosis due to perceived better support and care pathways (see Section 1.3.3.1).[9] Diagnostic delays can ultimately compromise prognosis and outcomes, with significant loss of lung function possible before diagnosis.[66, 67] This has been evidenced in a US retrospective study that found people with a delayed diagnosis of pulmonary fibrosis had poorer survival outcomes compared with those diagnosed in a timely manner (mortality rate: 16.6 [95% CI: 14.0, 19.6] and 12.5 [95% CI: 10.4, 14.9] per 100 person-years, respectively, p = 0.021).[67]

1.3.3 Humanistic and economic burden of disease

1.3.3.1 Humanistic burden

1.3.3.1.1 Burden of disease

The initial presentation of pulmonary fibrosis typically includes unexplained chronic breathlessness during exertion, a persistent dry (non-productive) cough, inspiratory crackles and digital clubbing (a deformity of the finger nails or toe nails).[10, 31, 68] Pulmonary function testing in suspected cases subsequently reveals a loss in pulmonary function, characterised by reduced FVC and decreased DL_{CO}.[10] As the disease progresses and pulmonary function further declines, breathlessness, coughing, mobility and the ability to conduct physical activity worsen and patients may ultimately become dependent on oxygen to help them breathe.[9, 69, 70] Recent patient-reported data from the Pulmonary Fibrosis Trust survey (PFT; December 2025) that have been provided to Boehringer ahead of publication indicate

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substantial functional impairment, with [redacted] of respondents reporting reduced daytime functioning and energy, and some unable to walk beyond 50 metres without oxygen desaturation below 90%.[71]

In addition to respiratory symptoms, fatigue is common and can be associated with further functional impairment, loss of independence and social isolation, which may lead to depression.[8, 9, 72] Anxiety and depression are commonly reported by patients and carers due to the unpredictable but ultimately progressive disease trajectory and limited treatment options (see Section 1.3.4).[8, 36] This is consistent with findings from the PFT 2025 survey, in which [redacted] of respondents reported anxiety, depression, or feelings of isolation, with patient comments reflecting profound emotional distress, including constant fear of suffocation and overwhelming psychological burden.[71]

Furthermore, comorbidities – both respiratory and non-respiratory – are common in people living with pulmonary fibrosis.[30, 73] In the UK, up to 84% of patients with pulmonary fibrosis have been reported to have at least one comorbidity, with common comorbidities including hypertension, ischaemic heart disease, gastro-oesophageal reflux disease and diabetes.[23, 37, 74]

The APF 2023 survey highlighted the profound physical and psychological impact of a pulmonary fibrosis diagnosis on both patients and their caregivers.[9] Multiple people reported they would prefer to have a cancer diagnosis, citing the lack of support within the healthcare system for patients with pulmonary fibrosis and delays in diagnosis (see Section 1.3.2). The report, along with the PFT 2025 survey, found that the rapid progression of symptoms – particularly breathlessness and the inability to engage in physical activity – markedly impacts patients' mental health and their overall quality of life. The physical burden of living with lung disease was described by one person diagnosed with IPF as follows: *"Breathlessness can feel like having a 25kg sack of sand tied around your chest. You cough a thousand times a day, you can't find your next word, you stumble out of exhaustion, you feel like a zombie"*; and "[redacted]".[9, 71] The emotional burden of living with pulmonary fibrosis is captured in key words used by respondents to the APF 2023 survey, which include: *"depressed"*, *"anxious"*, *"stressed"*, *"not coping"*, *"isolated"*, *"worried"*, *"scary"*, *"alone"*.[9]

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As part of APF's *Every Breath Counts* campaign, patients and caregivers described pulmonary fibrosis as a severely debilitating and progressive condition, frequently characterised using terms such as *"unfair", "horrific", "cruel", and "relentless",* reflecting the substantial physical and emotional burden of the disease.[75-79] This intense emotional burden was echoed in the PFT 2025 survey with respondents stating [redacted].[71]

Concerns shared in the APF 2023 and PFT 2025 surveys were echoed by patient experts at previous NICE Committee meetings, who described how pulmonary fibrosis severely affects mobility, mental health and the ability to carry out daily activities.[80]

The burden of pulmonary fibrosis extends to caregivers; approximately [redacted] of patients rely on caregivers every day according to the PFT 2025 survey, with many patients stating they had become dependent on caregivers for almost all daily activities.[71] Multiple responders highlighted the emotional strain placed on caregivers, including partners taking on the full caring role and experiencing exhaustion and struggling with the unpredictability of the disease trajectory.[71] A Delphi panel found that 85–90% of experts agreed that unpaid caregivers of patients with PPF experience reduced quality of life, particularly in areas such as sleep, emotional wellbeing, daily activities, social life and financial stability.[12]

The stress and anxiety relating to living with pulmonary fibrosis is further exacerbated for people who become dependent on oxygen to help them breathe (and their caregivers).[9, 11, 69] The British ILD service evaluation report suggests that all people with ILD should have access to oxygen services as required.[60] However, obtaining and maintaining oxygen supplies, particularly ambulatory oxygen, poses a real challenge.[9, 11, 69] Even with access to oxygen, many people with IPF limit leaving home due to concerns about equipment reliability, the physical burden of heavy devices, and the extensive planning required to manage limited oxygen supply, making everyday trips challenging.[9, 11, 69] Inside their homes, people with pulmonary fibrosis have reported being on oxygen therapy as like being *"on a leash"* and equipment creating potential hazards in the home.[11] In the PFT 2025 survey, around

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[redacted]of respondents were currently using oxygen to help them breathe with many requiring 24/7 support. Of those receiving oxygen, [redacted] reported that its use restricted their ability to travel or socialise, and [redacted] experienced stigma using oxygen in public, heightening their feelings of social isolation and reduced quality of life.[71] Patients described significant limitations from equipment weight, tubing, battery life, and fear of running out of oxygen with one patient stating [redacted].[71]

1.3.3.1.2 Burden of treatment

While the introduction of current AF therapies into the clinical care pathway has improved disease management to some extent by slowing the decline in lung function, treatment options for patients with IPF and PPF remain very limited (see Section 1.3.4). Current AF therapies – pirfenidone and nintedanib – were introduced over a decade ago and while helpful in slowing disease progression, they can cause significant side effects and are not suitable for everyone.[17]

In clinical trials of nintedanib, gastrointestinal adverse events (AEs), particularly diarrhoea, were frequently observed. In the pivotal INPULSIS trial programme investigating nintedanib for the treatment of IPF, diarrhoea was reported in 62% of patients in the first 52 weeks of treatment, resulting in permanent dose reduction of nintedanib in 14% of patients and discontinuation of nintedanib in 7% of patients.[13] Across all AEs, 24% of patients had to have a treatment interruption due to AEs, 16% of patients had to have a permanent dose reduction due to AEs and 19% of patients had to discontinue treatment due to AEs.[13]

In a narrative review of real-world safety data with nintedanib use, diarrhoea was reported in 32−79% of patients treated with nintedanib, and while most cases were mild to moderate intensity, one study reported up to 22% of patients experienced severe diarrhoea.[14] These data better reflect real-world experience of nintedanib use in the UK with clinical experts suggesting discontinuation due to severe diarrhoea rates with nintedanib in clinical practice is *"a lot higher"* than observed in clinical trials.[81] In the real-world safety data set, nausea or vomiting were also reported in up to 53% of patients treated with nintedanib (range: 2–53%) and weight loss was reported in up to 32% of patients (range: 5–32%).[14] Treatment interruption,

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permanent dose reduction and treatment discontinuation rates due to AEs of nintedanib varied widely but were reported in up to 42% (range: 5–42%), 37% (range: 13–37%) and 53% (range: 4–53%) of patients, respectively.[14] In a UK study, 69/154 patients (45%) discontinued nintedanib treatment due to AEs, and nearly half of these patients (47%) discontinued nintedanib within the first 3 months of treatment.[82]

Post-marketing data for nintedanib further report high rates of diarrhoea and treatment discontinuation due to diarrhoea. Data were collected on 157,775 patients who were treated with nintedanib for ILDs between 2014 to 2023. Over half of these patients (55%) experienced diarrhoea – 23% of patients discontinued treatment due to diarrhoea and a further 8% of patients had a dose reduction due to diarrhoea.[15]

Safety and tolerability is also a concern with pirfenidone (which is only licensed in IPF). It is estimated that 30% of patients are unsuitable for pirfenidone therapy due to upfront tolerability concerns[18] and a further ~40% of patients discontinue pirfenidone within the first year of treatment due to AEs.[16] In clinical trials of pirfenidone, the most frequent AEs observed were gastrointestinal and skin-related events. In the pivotal ASCEND and CAPACITY (004 and 006) trials, the most commonly reported AEs associated with pirfenidone included nausea (32.4%), rash (26.2%) and diarrhoea (18.8%).[16] These findings are consistent with longer-term open-label extension study data, which continue to identify nausea (28.8%) and diarrhoea (22.9%) as frequently observed AEs, alongside respiratory events.[16]

These observations align with findings from a nationwide French study (covering 99% of the population), which showed that approximately one-third of patients discontinued therapy with current AFs within the first year, with overall persistence at 1 year being 71% for IPF and 69.2% for PPF.[19] Similar results were observed in a multicentre Spanish study of real-world nintedanib use, where treatment discontinuation rates were 24.9%.[20]

Patient accounts from the PFT 2025 survey reinforce the limitations associated with current AF therapy. Nearly [redacted] of respondents receiving current AFs reported significant gastrointestinal adverse effects, including sudden diarrhoea, persistent nausea, appetite loss and weight reduction, which interfered with mobility,

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confidence and the ability to undertake normal daily activities.[71] Several patients described being effectively housebound due to unpredictable symptoms causing persistent anxiety when outside the home, with one noting, "[redacted]", and another reporting, "[redacted]". Patients also describe the difficulty in maintaining nutrition, with substantial weight loss reported ("[redacted]").[71] These tolerability challenges were a key driver of treatment discontinuation with [redacted] of respondents considering stopping treatment due to side effects.[71]

Similarly, in a different survey conducted by the APF charity in 2024 that have been provided to Boehringer ahead of publication, approximately [redacted] of patients receiving current AFs reported side effects and [redacted] of patients reported multiple side effects.[83] The most common side effects reported were diarrhoea ([redacted]), decreased appetite ([redacted]), nausea ([redacted]) and weight loss ([redacted]).[83]

Nintedanib and pirfenidone also require regular liver function monitoring due to cases of drug-induced liver injury (DILI) being reported with their use, including severe liver injury with fatal outcome, and elevated transaminases.[84-87] Nintedanib requires monthly liver tests for the first 3 months, followed by regular checks as clinically indicated – many centres recommend quarterly thereafter in the UK[88, 89]; pirfenidone requires monthly liver function monitoring for 6 months, followed by quarterly checks.[90] Liver function monitoring schedules necessitate frequent healthcare visits, which can be particularly challenging for patients with mobility issues, those requiring oxygen and/or experiencing severe breathlessness or those living far from ILD specialist centres. Data from the PFT 2025 survey reinforces this burden with many patients suggesting the management of transport, oxygen equipment and fatigue added further strain and, for some, discouraged continuation of therapy.[71] Beyond the personal impact, liver function monitoring further increases pressure on outpatient services, laboratory capacity and clinical staff time, contributing to the overall resource burden of managing IPF and PPF.[81]

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New treatment options with improved safety and tolerability are critical, not only to improve patient quality of life but also to enable longer time on treatment and therefore greater potential for sustained disease control and survival (see Section 1.3.5).

1.3.3.2 Economic burden

Globally, the costs associated with pulmonary fibrosis are substantial. The high prevalence of comorbidities, along with the challenges in diagnosing, monitoring and managing pulmonary fibrosis complicates treatment pathways and drives up expenses related to medication, healthcare resource use (HCRU) and non-medical costs.[12, 60, 91, 92] Key contributors to high HCRU costs include inpatient hospitalisations and respiratory support needs, particularly supplemental oxygen therapy.[92]

Given the lack of UK-based economic data for IPF and PPF, additional data to show HCRU are based on the FIBRONEER trials (see Section 3.5) and are validated by UK-based consultant respiratory physicians.[93] Resource use data from the FIBRONEER trials demonstrated a clear, progressive increase in healthcare utilisation with declining lung function in IPF and PPF. This trend was consistent across hospital-based care, primary care and specialist services. In both conditions, patients with pulmonary function impairment <40% FVC predicted incurred substantially higher rates of hospital admissions compared with those with pulmonary function ≥ 110% FVC predicted. Non-intensive-care-unit hospital admission rates in advanced disease were approximately threefold higher in IPF and nearly tenfold higher in PPF relative to the best-functioning group. Accident & Emergency attendance also increased markedly, indicating escalating acute care needs. Primary care utilisation remained significant across all stages, with general practitioner visit rates of 0.11–0.24 per quarter in IPF and 0.12–0.25 per quarter in PPF, reflecting continuous management requirements. Specialist consultations rose sharply with disease progression, particularly in PPF, where rates more than tripled from mild to severe stages of disease (based on FVC % predicted). Nurse visits also demonstrated a similar upward trend in IPF but remained low in PPF trial data. Additionally, patients with severe pulmonary fibrosis (FVC < 50% predicted) may require lung transplantation, which is associated with significant cost to the NHS.

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In addition to its economic burden on the NHS, supplemental oxygen therapy also places a significant burden on patients themselves. At a recent (2024) pulmonary fibrosis patient advisory board, patients talked about the struggle of managing the financial demands of oxygen therapy.[94] A systematic literature review (SLR) of qualitative evidence on the barriers to and facilitators of the use of oxygen therapy in people living with ILD similarly reported substantial out-of-pocket expenses associated with oxygen therapy, especially related to equipment, supply and running (electricity) costs.[11]

From a wider societal perspective, work productivity can be impacted by pulmonary fibrosis, with a greater negative impact observed in PPF compared with IPF due to the younger average age at diagnosis. In the UK Disease Specific Programme RWD (2024), [redacted] of patients with PPF were retired versus [redacted] of patients with IPF; however, retirement attributable to disease was notably more frequent in PPF ([redacted]) than in IPF ([redacted]).[36] Additionally, workplace adaptation due to illness was reported by [redacted] of patients with PPF, compared with [redacted] of those with IPF, highlighting the considerable loss of workforce participation and productivity associated with PPF.[36]

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1.3.4 Clinical pathway of care

1.3.4.1 Idiopathic pulmonary fibrosis care pathway

Figure 3 presents the treatment algorithm of IPF in England and Wales, based on the NICE clinical guideline for diagnosis and management of IPF in adults and more recent NICE technology appraisals of treatments for IPF.

Active treatment options (that is, disease-modifying pharmacological interventions for IPF) recommended by NICE are currently limited to:

- Nintedanib for patients with IPF with an FVC between 50% and 80% predicted [TA379][18] or an FVC > 80% predicted [TA864][80]
- Pirfenidone for patients with IPF with an FVC between 50% and 80% predicted [TA504][51]

Both of these treatments are AF therapies, but they have different mechanisms of action. Nintedanib is a small molecule tyrosine kinase inhibitor with AF effects that binds competitively to the adenosine triphosphate binding pocket of kinases involved in the pathogenesis of fibrotic tissue remodelling in ILDs.[84] Pirfenidone is an immunosuppressant with AF and anti-inflammatory effects, although its exact mechanism of action has not been fully established.[90]

In real-world practice, the decision on which current AF therapy (nintedanib or pirfenidone) is used to treat individual patients is made on a case-by-case basis with the benefits and disadvantages of both treatment options discussed. The discussion considers factors such as:

- FVC % predicted – pirfenidone is only reimbursed for patients with an FVC between 50% and 80% of that predicted, whereas nintedanib is also reimbursed for patients with an FVC % predicted above 80%
- Side-effect profile – both nintedanib and pirfenidone are associated with considerable safety and tolerability concerns that are fully discussed with patients (see Section 1.3.3.1.2)
- Administration burden – pirfenidone is taken three times daily (oral) and requires an initiation titration regime, whereas nintedanib is taken twice daily (oral)

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- Monitoring burden – for pirfenidone, liver function monitoring is required monthly for 6 months and as clinically indicated thereafter; for nintedanib liver function monitoring is required monthly for 3 months and as clinically indicated thereafter

If patients are started on one of these current AF therapies but need to discontinue due to progression of disease or tolerability concerns, they may be switched to the other current AF therapy (if eligible).[36] RWD suggest the volume of treatment-switching in the UK is low[36] and the more likely management approach is for patients who discontinue therapy with current AFs to receive best supportive care (BSC) only. However, clinical experts report that up to 20% of people with IPF switch between nintedanib and pirfenidone before moving to BSC.[93]

BSC is routinely offered to all patients and encompasses a range of interventions aimed at optimising quality of life.[95] This includes patient education and support, symptom management, oxygen therapy, treatment of comorbidities, pulmonary rehabilitation (where available) and access to palliative care services.[62] BSC is also given to patients whose pulmonary function declines to FVC < 50% predicted who have no active treatment options, and patients who are not suitable for current treatment options, or have progressed despite treatment with current AFs. This includes patients who could not start and/or have had to discontinue AF therapy due to tolerability concerns (see Section 1.3.5).

Patients whose pulmonary function declines to FVC < 50% predicted may be candidates for a lung transplant given the severity of their disease[18, 62]; however, internal estimates and the FIBRONEER trial programme suggest that a very small proportion of patients with IPF or PPF ultimately undergo lung transplantation – around [redacted].[21, 22] This is supported by < 5% lung transplantation referral rates captured in the British Thoracic Society (BTS) ILD Registry.[23]

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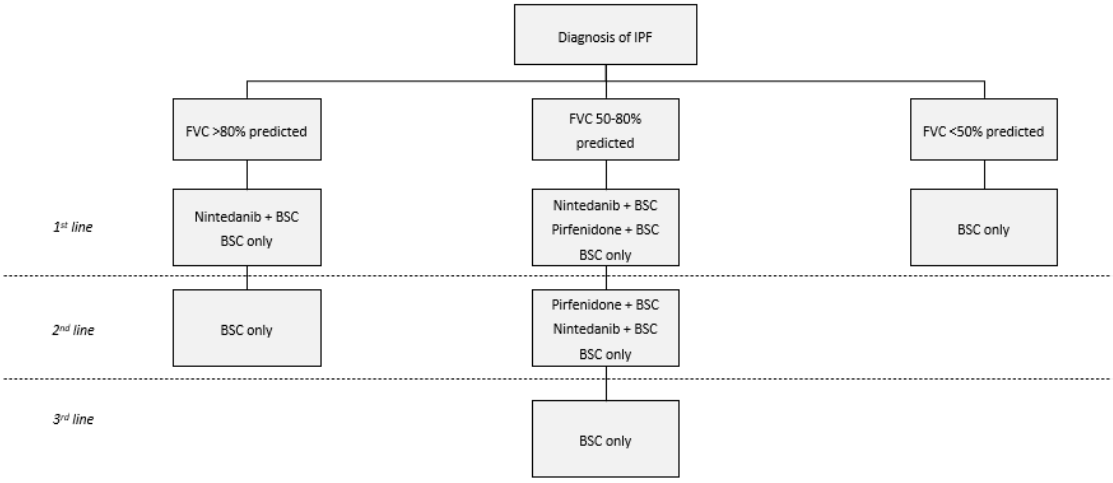
Figure 3: Care pathway for IPF in England and Wales



Key: BSC, best supportive care; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.
Source: Adapted from NICE (CG163)[62]; NICE (TA864)[80];NICE (TA379)[18]; NICE (TA504).[51]

RWD from the British ILD Registry (2024) reported that 72% of patients with IPF received AF therapy at presentation, with most (51%) being prescribed nintedanib.[37] These are reasonably consistent with Disease Specific Programme RWD (2024) that report [redacted] of patients with IPF were treated with AF therapy at presentation, and of these patients, [redacted] were prescribed nintedanib.[36]

Clinical expert opinion in England indicates that AF prescribing in IPF is strongly influenced by pulmonary function, as measured by FVC % predicted.[93] Treatment use estimates from clinical experts were generally higher than reported in RWD but views varied on exact proportions, highlighting the heterogeneity in current IPF management. All agreed that nintedanib use is highest in people with pulmonary function > 80% FVC predicted, with 80–90% of such patients receiving therapy. Use was estimated to decline to 60–76% in people with pulmonary function 50–80% FVC predicted and is generally stopped in people with pulmonary function < 50% FVC predicted. Pirfenidone use was estimated at 19–30% of people with pulmonary function 50–80% FVC predicted, with no use reported in people with pulmonary function >80% FVC predicted or <50% FVC predicted for whom pirfenidone is not reimbursed in the UK.

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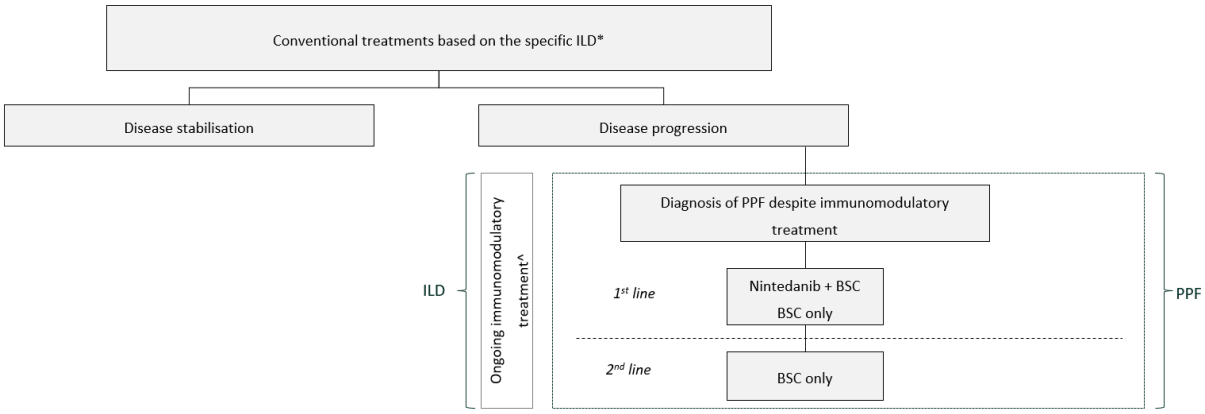
1.3.4.2 Progressive pulmonary fibrosis care pathway

Figure 4 presents the treatment algorithm of PPF in England and Wales. There are no dedicated clinical guidelines in the UK for managing PPF and only one previous NICE technology appraisal.

The only active treatment option (that is, disease-modifying pharmacological intervention for PPF) recommended by NICE is nintedanib.[47]

Before identification of PPF, care will be targeted to the underlying ILD diagnoses. This commonly includes immunomodulatory therapy (in diseases with immune pathologies), such as immunosuppressants, corticosteroids, infliximab or rituximab or reducing exposure in exposure-related ILDs. Immunomodulatory treatments aim to reduce inflammation and slow disease progression in ILDs where inflammation is a key driver of pulmonary fibrosis.[47] They are not licensed to treat PPF and there is no evidence to show that these treatments slow the progression of pulmonary fibrosis. For people whose ILD progresses to PPF and who are offered nintedanib therapy to treat PPF, immunosuppressive therapy may be continued or tapered, depending on the clinical context and independently from the decision to start nintedanib. BSC is also routinely offered to all patients, aligned to the IPF care pathway.[95]

Figure 4: Care pathway for PPF in England and Wales



Key: BSC, best supportive care; ILD, interstitial lung disease; PPF, progressive pulmonary fibrosis.
Notes: *Including, but not limited to, immunosuppressants (mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate), corticosteroids, infliximab or rituximab; ^some but not all patients may continue to receive ongoing immunomodulatory treatment for underlying ILD.
Source: adapted from NICE (TA747).[47]

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RWD from the British ILD Registry (2024) reported that 40% of patients with PPF received AF therapy at presentation.[37] These are reasonably consistent with Disease Specific Programme RWD (2024) that report [redacted] of patients with PPF were treated with AF therapy.[36] Corticosteroid use was reported in [redacted] and immunosuppressant use in [redacted] of patients with PPF, reflecting the concomitant use of immunomodulatory therapy and AF therapy in current practice.[36]

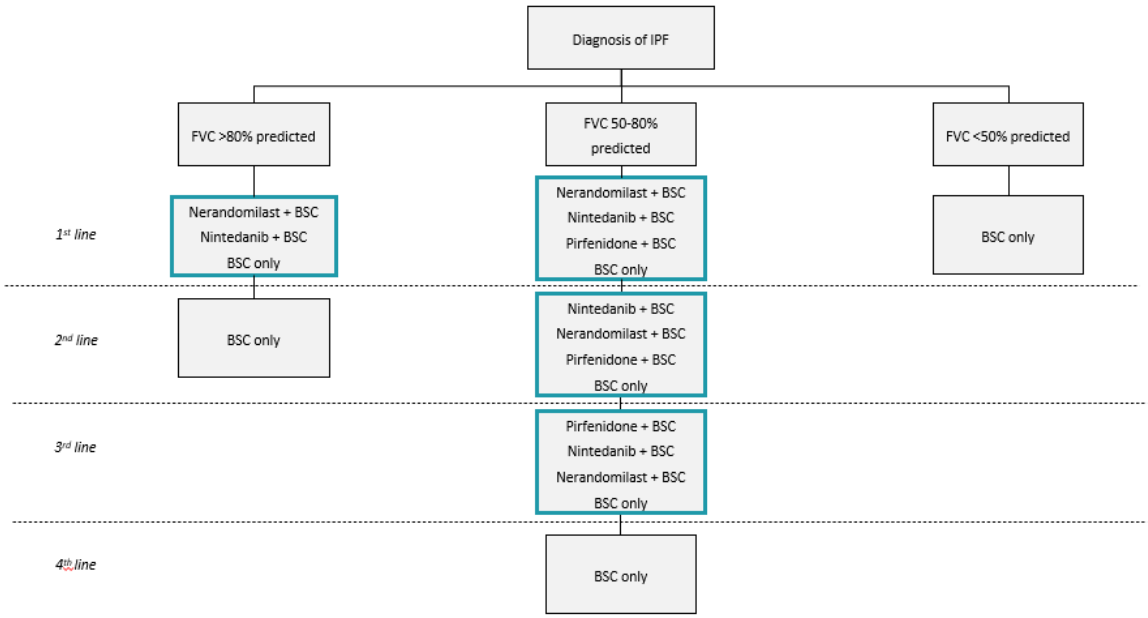
Clinical expert opinion indicates these data are at the lower end of real-world use and estimates that 40–70% of patients with PPF receive nintedanib therapy in the UK, with the remaining 30–60% managed with BSC or other non-AF approaches.[93]

1.3.4.3 Proposed positioning of nerandomilast

Nerandomilast offers a novel treatment option for patients with IPF and PPF. It is intended to be used as a monotherapy for the treatment of pulmonary fibrosis but can be used concomitantly with BSC and in the case of PPF, with immunomodulatory treatment for the underlying ILD diagnosis.

The proposed positioning of nerandomilast in the care pathway is shown in Figure 5 for IPF and in Figure 6 for PPF.

Figure 5: Proposed positioning of nerandomilast in the care pathway for IPF



Key: BSC, best supportive care; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.

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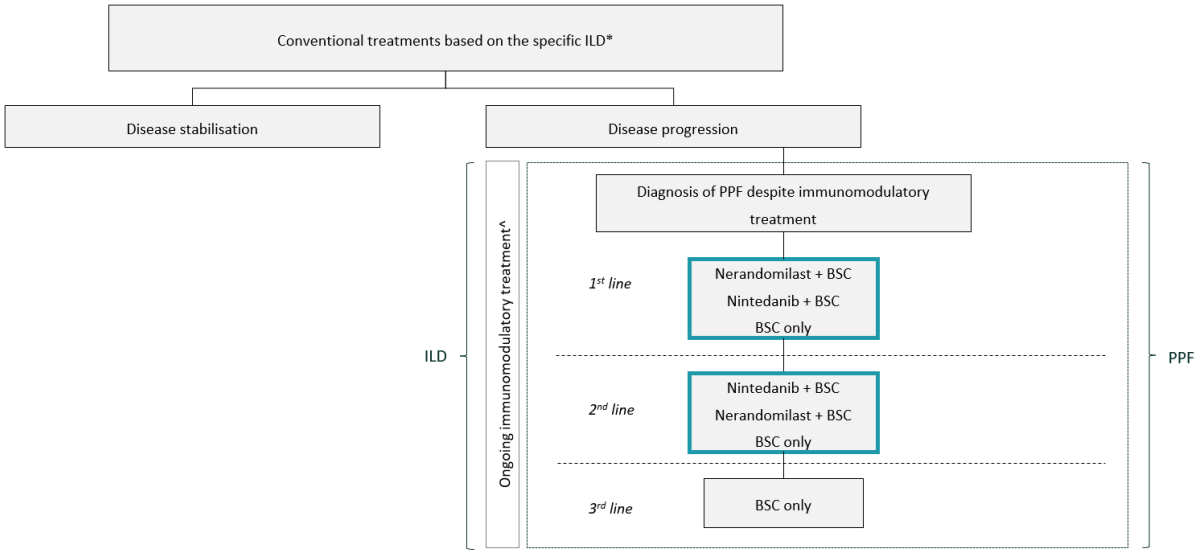
Figure 6: Proposed positioning of nerandomilast in the care pathway for PPF



Key: BSC, best supportive care; ILD, interstitial lung disease; PPF, progressive pulmonary fibrosis.
Notes: *Including, but not limited to immunosuppressants (mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate), corticosteroids, infliximab or rituximab; ^some but not all patients may continue to receive ongoing immunomodulatory treatment for underlying ILD.

Clinical experts in the UK indicate that early initiation of treatment with nerandomilast (i.e. first-line therapy for newly diagnosed patients) may have the highest potential for benefit, based on the FIBRONEER-IPF and FIBRONEER-ILD results (see Section 2).[81] They also considered the patient perspective and anticipate strong preference for an effective treatment option that avoids frequent liver function monitoring, offers a better safety and tolerability profile and demonstrates positive impact on survival, further supporting early initiation of nerandomilast.[81]

1.3.5 Unmet need

IPF and PPF are chronic, progressive forms of ILD characterised by an irreversible decline in lung function associated with high morbidity and early mortality, despite current standard of care.[1, 9] Beyond the physical burden, individuals living with pulmonary fibrosis and their carers report high practical and emotional burden relating to the complex diagnostic and management pathway (see Sections 1.3.2 and 1.3.4) and the progressive disease trajectory (see Section 1.3.1.3).

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For those people who do get diagnosed and access treatment via specialist ILD centres, there are still unmet needs relating to treatment effectiveness, safety and tolerability. Current AF therapies can slow the rate of disease progression, but median survival following diagnosis of IPF or PPF remains very poor, at approximately 3.5–5 years, underscoring the limited long-term effectiveness of current standard of care.[1, 9] The 5-year survival rate of 45% associated with pulmonary fibrosis is lower than the 5-year survival rates of many common cancers, which have markedly improved over the last decade.[9, 96] In addition, current AF therapies are associated with safety and tolerability concerns that frequently lead to dose reductions and treatment discontinuation (see Section 1.3.3.1.2). These issues can limit their ability to provide sustained disease control and place additional pressure on ILD services, due to the need for ongoing monitoring, management of AEs, repeated dose adjustments, and increased patient support.

The profound physical, practical and emotional burden of living with pulmonary fibrosis markedly affects the quality of life of patients and carers. Qualitative research and patient organisation reports highlight the significant challenges faced every day (see Section 1.3.3.1) with some patients stating they would rather receive a cancer diagnosis than a diagnosis of pulmonary fibrosis, given the lack of support within the healthcare system and stark prognosis.[9] Patients and their carers face every day in fear – fear of worsening disease and suffocation, fear of running out of oxygen, fear of uncontrollable diarrhoea and weight loss, fear of public stigma if they leave the house, and so it goes on.[9, 71]

People living with IPF and PPF have a clear and urgent unmet need for an effective, safe and well tolerated new treatment options that can enable longer time on treatment to slow disease progression, extend life, and preserve the overall HRQL of patients. The need for new drug treatment and improved survival were two of five key areas of stakeholder priorities for the diagnosis and management of pulmonary fibrosis, highlighting this clear and urgent unmet need.[97]

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1.4 Equality considerations

Regional disparities in access to care may arise due to the limited number and geographic distribution of ILD specialist centres in the UK – in total there are only 26 centres across England and Wales, and some regions only have one centre to service all local patients, e.g. in the North East.[9] This presents two key challenges: accessing specialist services and maintaining persistence on the ILD care pathway, as logistical barriers can hinder ongoing engagement (in a UK-based analysis, around 1 in 10 patients referred to a specialist ILD centre were unable to travel for care[98]). This is heightened in more socio-economic deprived areas where people living with IPF and PPF may not be able to cover the cost of regular visits to ILD specialist centres. This has previously been cited as a major barrier for deprived populations, compounding inequities in healthcare.[99]

Socio-economic status also impacts access to supportive services such as pulmonary rehabilitation, oxygen therapy and palliative care, which are often not funded by the NHS.[60] While the impact of ethnicity on equity is difficult to establish due to inconsistent coding in available datasets, socio-economic-status-related barriers remain a significant concern.

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2 Clinical effectiveness

- Nerandomilast offers a first in class PDE4B inhibitor treatment option for people living with IPF or PPF that delivers AF and immunomodulatory effects, with the potential to improve OS and quality of life[29]
- The FIBRONEER trial programme provides robust randomised controlled trial evidence for nerandomilast versus placebo, representing BSC[28, 100]
- In total, 2,355 diverse patients were enrolled across FIBRONEER-IPF and FIBRONEER-ILD, of which 307 were treated with nerandomilast 18 mg bid monotherapy and 310 were treated with placebo monotherapy[28, 100]
- In pooled analyses of FIBRONEER-IPF and FIBRONEER-ILD, nerandomilast 18 mg bid monotherapy was shown to significantly[101]:
  - Slow disease progression, with an adjusted mean difference in change from baseline to Week 52 in FVC of [redacted] (95% CI: [redacted]) versus placebo, representing a [redacted] relative reduction in lung function decline
  - Reduce the risk of time to acute exacerbation, hospitalisation for respiratory cause or death versus placebo by [redacted] (HR: [redacted])
  - Reduce the risk of acute exacerbation or death versus placebo by [redacted] (HR: [redacted])
  - Reduce the risk of hospitalisation for respiratory cause or death versus placebo by [redacted] (HR: [redacted])
  - Reduce the risk of death versus placebo by [redacted] (HR: [redacted])
  - Extend the periods of progression-free living, reducing the risk of time to FVC % predicted decline of > 10% or death versus placebo: HR: [redacted]
- Nerandomilast 18 mg bid monotherapy was also well tolerated with lower rates of serious AE, fatal AEs and AEs leading to treatment discontinuation versus placebo[28, 100]
- In robust individual patient-level data (IPD) based indirect treatment comparison (ITC) nerandomilast 18 mg bid monotherapy demonstrated[102]:
  - A clinically meaningful reduction in the risk of death of [redacted] in the IPF population and [redacted] in the PPF population versus current AF therapy

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- A similar effect on reduction in lung function decline versus current AF therapy
- A significant reduction in the risk of experiencing a gastrointestinal AE of [redacted] in the IPF population and [redacted] in the PPF population versus current AF therapy
- A clinically meaningful reduction in the risk of treatment discontinuation due to AE of [redacted] in the IPF population and [redacted] in the PPF population versus current AF therapy
- A significantly longer time to treatment discontinuation (TTD) versus current AF therapy

- Nerandomilast provides a much-needed treatment option for individuals with IPF and PPF, offering a safe and well-tolerated therapy that slows disease progression, prolongs survival, and helps maintain HRQL
  - It's introduction into the care pathway would be (strongly) welcomed by the clinical community[81]

2.1 Identification and selection of relevant studies

See Appendix B for full details of the process and methods used to identify and select the clinical evidence relevant to nerandomilast.

2.2 List of relevant clinical effectiveness evidence

Table 4 summarises the clinical effectiveness evidence supporting nerandomilast for the treatment of adult patients with IPF.

Table 4: Clinical effectiveness evidence

Study	**FIBRONEER-IPF (NCT05321069)**	**FIBRONEER-ILD (NCT05321082)**	**NCT04419506**
Study design	Randomised, double-blind, placebo-controlled trial evaluating the efficacy and safety of nerandomilast (9 mg or 18 mg) over at least 52 weeks in patients with IPF.	Randomised, double-blind placebo-controlled trial evaluating the efficacy and safety of nerandomilast (9 mg or 18 mg) over at least 52 weeks in patients with PPF.	Randomised, double-blind, placebo-controlled parallel group study in patients with IPF over 12 weeks evaluating efficacy, safety and tolerability of nerandomilast taken orally.

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Study	**FIBRONEER-IPF (NCT05321069)**	**FIBRONEER-ILD (NCT05321082)**	**NCT04419506**
Population	Adults with IPF	Adults with PPF	Adults with IPF
Intervention(s)	Nerandomilast (9 mg or 18 mg bid) + patients' standard of care treatment.	Nerandomilast (9 mg or 18 mg bid) + patients' standard of care treatment.	Nerandomilast (18 mg bid) + patients' standard of care treatment.
Comparator(s)	Placebo (matching the nerandomilast tablets) + patients' standard of care treatment.	Placebo (matching the nerandomilast tablets) + patients' standard of care treatment.	Placebo (matching the nerandomilast tablets) + patients' standard of care treatment.
Indicate if study supports application for marketing authorisation	Yes ✓ No	Yes ✓ No	Yes No ✓
Indicate if study used in the economic model	Yes ✓ No	Yes ✓ No	Yes No ✓
Rationale if study not used in model	N/A	N/A	The duration of the trial was only 12 weeks.
Reported outcomes specified in the decision problem	**Pulmonary / physical function** • Absolute change from baseline in FVC (absolute change [ml] and change in % predicted) and DL_{CO} % predicted • Time to first occurrence of any of the components of the composite endpoint: acute IPF exacerbation, hospitalisation for respiratory cause or death • Time to absolute decline in FVC % predicted of > 10% /DL_{CO} % predicted of > 15% • Absolute change from baseline in L-PF symptom scores • Use of supplemental oxygen **Exacerbation rate** • Time to first acute IPF exacerbation Hospitalisation rate • Time to first acute hospitalisation for respiratory cause		Pulmonary function • Absolute change from baseline in FVC • Adverse effects of treatment

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Study	**FIBRONEER-IPF (NCT05321069)**	**FIBRONEER-ILD (NCT05321082)**	**NCT04419506**
	Mortality • Time to death **Health-related quality of life** • EQ-5D VAS **Adverse effects of treatment**		

Key: bid, twice a day; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; L-PF, Living with Pulmonary Fibrosis questionnaire; N/A, not applicable; PPF, progressive pulmonary fibrosis.
Notes: Bolded outcomes are those used in the economic modelling.
Source: Maher et al. 2025[100]; Richeldi et al. 2022[26]; Richeldi et al. 2025.[28]

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2.3 Summary of methodology of the relevant clinical effectiveness evidence

Appendix I provides summaries of the trial methodology for FIBRONEER-IPF and FIBRONEER-ILD.

FIBRONEER-IPF and FIBRONEER-ILD were randomised, placebo-controlled, double-blind Phase III studies in patients with IPF and PPF, respectively. The studies were designed to evaluate the efficacy and safety of nerandomilast (9 mg or 18 mg) twice a day (bid) compared with placebo over at least 52 weeks in the respective populations in addition to the patients' standard of care treatment.

In this submission, FIBRONEER-IPF and FIBRONEER-ILD data are only presented for a sub-population – the 'no AF background therapy' cohort – aligning to the intended use of nerandomilast as monotherapy only. The dosing of focus in this submission is nerandomilast 18 mg bid, aligning to the marketing authorisation application in the UK. Data for the nerandomilast 9 mg bid treatment arm are also presented in tables and figures, as this dose will be available for patients unable to tolerate the 18 mg bid dosing.

Figure 7 presents the study schema for FIBRONEER-IPF and FIBRONEER-ILD. Patients were randomised in a 1:1:1 ratio to either nerandomilast 9 mg bid, nerandomilast 18 mg bid or placebo in addition to patients' standard of care. They then entered the treatment phase for at least 52 weeks. Randomisation in both trials was stratified by the presence of AF background therapy (yes versus no), and additionally in FIBRONEER-ILD by the HRCT pattern ("UIP or UIP-like fibrotic pattern" versus "other fibrotic patterns"). Both trials were conducted in two parts. In Part A, patients received up to 52 weeks of randomised blinded treatment; after the last patient completed the Week 52 visit, the database lock 1 (DBL1) was taken for the main analysis. In Part B, patients received randomised blinded treatment beyond 52 weeks; after the last patient completed the end-of-treatment visit, the database lock 2 (DBL2) was taken for the final analysis (for further information on database locks and planned analyses, see Section 2.4). The maximum total treatment duration in FIBRONEER-IPF was 20.8 months at DBL1 and 22.9 months at the end of the

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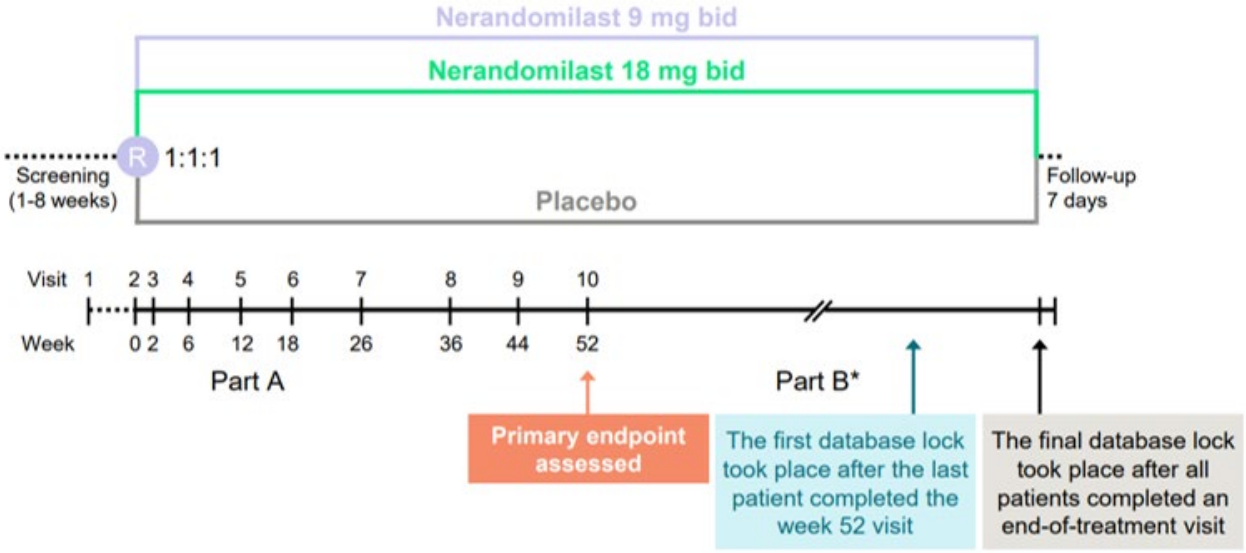
trial. The maximum total treatment duration in FIBRONEER-ILD was 25.0 months at DBL1 and 26.2 months at the end of the trial.

In both trials, the primary objective was to demonstrate a reduction in lung function decline as measured by the change from baseline in FVC (ml) at 52 weeks for nerandomilast compared with placebo in patients with IPF (FIBRONEER-IPF) and PPF (FIBRONEER-ILD). The key secondary objective was to demonstrate nerandomilast's superiority to placebo in reducing the risk of clinically meaningful events (defined in the key secondary endpoint as the time to the first occurrence of either first acute exacerbation, first hospitalisation for respiratory cause or death [whichever occurred first]). Further details of all endpoints are provided in Appendix I.

Figure 7: Study design overview for FIBRONEER-IPF and FIBRONEER-ILD



Key: bid, twice a day; CTR, clinical trial report.
Notes: *visits occurred every 12 weeks until the last patient completed 52 weeks of treatment.
Source: adapted from FIBRONEER-IPF CTR[103] and FIBRONEER-ILD CTR.[104]

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2.3.1 Patient disposition

In FIBRONEER-IPF, 1,720 participants were screened and 1,177 underwent randomisation; in FIBRONEER-ILD, 1,780 participants were screened and 1,178 underwent randomisation. All patients randomised comprised the full analysis set (FAS) of the respective trials.

Of all patients randomised in FIBRONEER-IPF, 262 (22.3%) make up the monotherapy population of interest to this submission. Of these patients, 87 were assigned to nerandomilast 18 mg bid, 88 were assigned to nerandomilast 9 mg bid and 87 were assigned to placebo. Of all patients randomised in the FIBRONEER-ILD trial, 662 (51.2%) make up the monotherapy population of interest to this submission. Of these patients, 220 were assigned to nerandomilast 18 mg bid, 220 were assigned to nerandomilast 9 mg bid and 222 were assigned to placebo.

Patient disposition figures for both trials are presented in Appendix B.2. For further information on database locks and planned analyses, see Section 2.4.

In FIBRONEER-IPF, [redacted] patients of the monotherapy population [redacted] completed the planned 52-week treatment period and [redacted] completed the planned treatment period over the whole trial. The most common reasons for premature discontinuation were [redacted] and [redacted]. In the nerandomilast 18 mg bid group (n = 87), [redacted] completed the planned 52-week treatment period and [redacted] completed the planned treatment period over the whole trial. The most common reasons for premature discontinuation in this group were [redacted]and [redacted].

In FIBRONEER-ILD, [redacted] patients of the monotherapy population completed the planned 52-week treatment period and [redacted] completed the planned treatment period over the whole trial. The most common reasons for premature discontinuation were [redacted] and [redacted]. In the nerandomilast 18 mg bid group (n = 220), [redacted] completed the planned 52-week treatment period and [redacted] completed the planned treatment period over the whole trial. Again, the most common reasons for premature discontinuation were [redacted]and withdrawal by subject [redacted].

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2.3.2 Patient baseline characteristics

Table 5 and Table 6 present patient baseline characteristics for the monotherapy population of FIBRONEER-IPF and FIBRONEER-ILD, respectively. For baseline characteristics of the FAS populations of FIBRONEER-IPF and FIBRONEER-ILD, please refer to Appendix K and L.

Demographics and baseline lung function parameters (FVC, DL_{CO} and baseline supplemental oxygen use) were generally aligned across treatment arms in both trials.[28, 100]

Of the monotherapy population of FIBRONEER-IPF, most were male (76.0%) and elderly (mean age: 70.4 years) [redacted] (Table 5). The mean time since IPF diagnosis was 2.8 years (standard deviation [SD]: 2.9) before the trial, and [redacted] had been diagnosed for more than 3 years.[103]

In FIBRONEER-ILD, the gender distribution was balanced with approximately half the monotherapy population being male (Table 6). The mean age was 66.2 years and [redacted]. The majority of the patients presented with a baseline UIP or UIP-like fibrotic pattern (71.6%). The mean time since PPF diagnosis was 4.0 years (SD: 4.1) before the trial, and [redacted] had been diagnosed for more than 3 years.[104]

On consultation at a UK advisory board, clinical experts confirmed the baseline characteristics of patients enrolled in the FIBRONEER trial programme (FAS populations) broadly reflect the pulmonary fibrosis population they treat in clinical practice.[81] However, they did note some differences in the underlying ILD diagnoses and a high proportion of ambiguous ‘UIP-like’ fibrotic patterns in the FIBRONEER-ILD population, as well as a higher-than-expected proportion of males. They also noted patients enrolled in FIBRONEER-IPF were slightly younger and had fewer comorbidities, but had a longer disease duration, than the typical UK patient (see Section 2.13).

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Table 5: Baseline characteristics of patients, FIBRONEER-IPF ('no AF background therapy' cohort)

Characteristic	Nera 18 mg bid N = 87	Nera 9 mg bid N = 88	Placebo N = 87	Total N = 262
Male sex, n (%)	68 (78.2)	63 (71.6)	68 (78.2)	199 (76.0)
Age, mean (SD), years	70.1 (8.8)	70.3 (8.4)	70.9 (8.2)	70.4 (8.4)
Weight, mean (SD), kg	71.86 (13.4)	73.41 (16.4)	74.4 (14.2)	73.23 (14.7)
Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Black/African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Multiple, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)[a]				
Never smoked	29 (33.3)	25 (28.4)	23 (26.4)	77 (29.4)
Former smoker	56 (64.4)	60 (68.2)	61 (70.1)	177 (67.6)
Current smoker	2 (2.3)	3 (3.4)	3 (3.4)	8 (3.1)
Time since diagnosis of IPF, mean (SD), years	2.93 (3.1)	2.78 (2.5)	2.78 (3.2)	2.83 (2.9)
FVC				
Mean value (SD), mL	2761.4 (778.4)	2763.6 (739.3)	2833.3 (885.7)	2786 (800.9)
Mean % predicted (SD)	82.1 (18.7)	82.31 (15.7)	82.18 (19.5)	82.2 (17.9)
DL_{CO}, mean % predicted (SD)[b]	57.1 (18.4)	57.38 (18.5)	51.03 (17.5)	55.18 (18.3)
Previous AF use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
AF naïve, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Supplemental oxygen therapy, n (%)	14 (16.1)	11 (12.5)	17 (19.5)	42 (16.0)

Key: AF, antifibrotic; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; nera, nerandomilast; SD, standard deviation.
Notes: [a] Percentages may not total 100 because of rounding. [b] Values corrected for haemoglobin level.
Source: FIBRONEER-IPF CTR (Tables 15.1.7.6: 2–15.1.7.6: 4)[103]; Richeldi et al. 2025.[28]

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Table 6: Baseline characteristics of patients, FIBRONEER-ILD ('no AF background therapy' cohort)

Characteristic	Nera 18 mg bid N = 220	Nera 9 mg bid N = 220	Placebo N = 222	Total N = 662
Male sex, n (%)	111 (50.5)	103 (46.8)	116 (52.3)	330 (49.8)
Age, mean (SD), years	65.5 (10.2)	66.8 (10.2)	66.2 (10.8)	66.2 (10.4)
Weight, mean (SD), kg	70.4 (15.6)	70.3 (16.5)	70.5 (17.9)	70.4 (16.7)
Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Black/African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Multiple, n (%)	0 (0)	3 (1.4)	2 (0.9)	5 (0.8)
Smoking status, n (%)[a]				
Never smoked	114 (51.8)	127 (57.7)	123 (55.4)	364 (55.0)
Former smoker	98 (44.5)	88 (40.0)	94 (42.3)	280 (42.3)
Current smoker	8 (3.6)	5 (2.3)	5 (2.3)	18 (2.7)
Time since diagnosis of PPF, mean (SD), years	4.0 (4.2)	4.1 (4.4)	3.9 (3.6)	4.0 (4.1)
Underlying ILD diagnoses, n (%):				
Autoimmune ILDs	70 (31.8)	73 (33.2)	71 (32.0)	214 (32.3)
Hypersensitivity pneumonitis	30 (13.6)	42 (19.1)	39 (17.6)	111 (16.8)
Unclassifiable idiopathic interstitial pneumonia	40 (18.2)	44 (20.0)	36 (16.2)	120 (18.1)
Idiopathic non-specific interstitial pneumonia	55 (25.0)	42 (19.1)	40 (18.0)	137 (20.7)
Other ILDs	25 (11.4)	19 (8.6)	36 (16.2)	80 (12.1)
Baseline UIP or UIP-like fibrotic pattern	154 (70.0)	162 (73.6)	158 (71.2)	474 (71.6)
Other fibrotic pattern	66 (30.0)	58 (26.4)	64 (28.8)	188 (28.4)
FVC				
Mean value (SD), mL	2,354 (715)	2244 (759)	2264 (740)	2,287 (738)
Mean % predicted (SD)	72.4 (15.8)	70.9 (16.0)	70.1 (16.0)	71.1 (16.0)
DL_{CO}, mean % predicted (SD)[b]	52.8 (17.4)	52.3 (16.3)	52.4 (16.5)	52.5 (16.7)
Previous AF use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
AF naïve, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Supplemental oxygen therapy, n (%)	45 (20.5)	38 (17.3)	44 (19.8)	127 (19.2)

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Characteristic	Nera 18 mg bid N = 220	Nera 9 mg bid N = 220	Placebo N = 222	Total N = 662
Key: AF, antifibrotic; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IPD, important protocol deviations; nera, nerandomilast; PPF, progressive pulmonary fibrosis; SD; standard deviation; UIP, usual interstitial pneumonia. **Notes:** [a] Percentages may not total 100 because of rounding. [b] Values corrected for haemoglobin level. **Source:** FIBRONEER-ILD CTR (Tables 15.1.7.6: 2–15.1.7.6: 4);[104] Maher et al. 2025.[100]				

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Table 7 provides a summary of the statistical analysis and definitions of analysis sets in FIBRONEER-IPF and FIBRONEER-ILD.

The primary endpoint was analysed with the use of a mixed-effects model for repeated measures, with the following covariates: treatment at each visit, baseline AF background therapy (yes/no), continuous fixed effects for baseline FVC (mL) at each visit and HRCT pattern (UIP-like fibrotic pattern versus other fibrotic patterns) – FIBRONEER-ILD only.

Multiplicity-adjusted analyses were performed on the primary and key secondary endpoints and a graphical testing procedure was used to test the primary and key secondary endpoints for both nerandomilast dose levels. The hypothesis testing of the primary endpoint was based on Week 52 data; the hypothesis testing of the key secondary endpoint was based on the main analysis data collected up to the main analysis (all data up to DBL1). No adjustment for multiplicity was planned beyond primary and key secondary objectives, or beyond the main analysis. All other secondary endpoints conducted on DBL1, and all analyses conducted on DBL2 data are therefore considered exploratory in nature.

In this submission, FIBRONEER-IPF and FIBRONEER-ILD data are only presented for the ‘no AF background therapy’ cohort, aligning to the intended use of nerandomilast in the UK as monotherapy in people with IPF or PPF. This was a pre-specified subgroup (and a randomisation stratification factor) for primary and key secondary endpoints analysis, but the monotherapy population was not the basis of

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hypothesis testing and therefore all statistical testing should be considered exploratory in nature.

Table 7: Summary of statistical analyses for FIBRONEER-IPF and -ILD

Hypothesis objective	A graphical testing procedure (refer to Appendix J) was used to test the primary and key secondary endpoints for both dose levels. Statistical hypotheses tested for the primary endpoint were: • H01: there was no difference in the mean change from baseline in FVC in mL at Week 52 between nerandomilast 18 mg bid and placebo • Ha1: there was a difference in the mean change from baseline in FVC in mL at Week 52 between nerandomilast 18 mg bid and placebo • H02: there was no difference in the mean change from baseline in FVC in mL at Week 52 between nerandomilast 9 mg bid and placebo • Ha2: there was a difference in the mean change from baseline in FVC in mL at Week 52 between nerandomilast 9 mg bid and placebo The primary objective of the trial was to be achieved if either H01 or H02 was rejected Statistical hypotheses tested for the key secondary endpoint were: • H03: there was no difference in the time to first acute IPF/ILD exacerbation, first hospitalisation for respiratory cause or death between nerandomilast 18 mg bid and placebo • Ha3: there was a difference in the time to first acute IPF/ILD exacerbation, first hospitalisation for respiratory cause or death between nerandomilast 18 mg bid and placebo • H04: there was no difference in the time to first acute IPF/ILD exacerbation, first hospitalisation for respiratory cause or death between nerandomilast 9 mg bid and placebo vs • Ha4: there was a difference in the time to first acute IPF/ILD exacerbation, first hospitalisation for respiratory cause or death between nerandomilast 9 mg bid and placebo The hypothesis testing of the key secondary endpoint was based on data collected up to the main analysis (all data up to DBL1). A supplementary analysis of the key secondary endpoint using all data collected over the whole trial was performed after DBL2.

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Statistical analysis	The primary endpoint was the absolute change from baseline in FVC (mL) at Week 52. The primary endpoint was analysed with a REML based approach using an MMRM. The key secondary endpoint was time to the first occurrence of any of the components of the composite endpoint: time to first acute IPF (in FIBRONEER-IPF) or ILD (in FIBRONEER-ILD) exacerbation, first hospitalisation for respiratory cause, or death. The key secondary endpoint was analysed using a Cox proportional hazards model with data from the whole trial, i.e. including data beyond 52 weeks. To test the equality of hazard rates of nerandomilast groups vs placebo, the Wald test was used. A graphical approach was used as multiple testing procedure to test both doses vs placebo for the primary and key secondary endpoints. All other secondary endpoints and further endpoints were considered exploratory in nature and no adjustment for multiplicity was made.
Analysis sets	**Entered Set (ES)**: This patient set includes all patients who signed informed consent. The ES was used for the analyses of patient disposition. **Randomised Set (RS)**: This patient set includes all entered and randomised patients. The RS was used for the analyses of patient disposition. **Full Analysis Set (FAS)**: This patient set includes all randomised patients who received at least one dose of study drug. The FAS was used for baseline demographics and characteristics, protocol deviations, and all efficacy analyses, in which patients were analysed as their randomised treatment group. **Treated Set (TS)**: This patient set includes all randomised patients who received at least one dose of study drug. The TS was used for all safety analyses, in which patients were analysed according to the actual treatment they received. **PK parameter analysis set (PKS)**: This patient set includes those patients in the TS with at least one valid plasma concentration available.
Sample size, power calculation	**FIBRONEER-IPF (NCT05321069)** In the determination of sample size, the effect of nerandomilast 9 mg bid or 18 mg bid vs placebo on change from baseline in FVC at Week 52 was assumed to be 110 mL in patients not taking background therapy (based on trials of nintedanib) and lower (i.e. 65 mL) in patients taking background therapy. It was assumed that 70% of patients would take background therapy, resulting in an assumed effect of nerandomilast of 74 mL. The standard deviation was assumed to be 280 mL. Under the graphical testing procedure, it was estimated that a sample size of 963 patients (321 per treatment group) would yield approximately 90% power to detect a 74 mL between-group difference in the primary end point at a two-sided alpha level of 0.05.

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	FIBRONEER-ILD (NCT05321082) In the determination of sample size, the effect of nerandomilast 9 mg bid or 18 mg bid vs placebo on change from baseline in FVC at Week 52 was assumed to be 85–90 mL in patients not taking background nintedanib (based on trials of nintedanib) and lower (i.e., 55–60 mL) in patients taking background nintedanib. It was assumed that 30% of patients would take background nintedanib at baseline, and that among patients not taking background nintedanib at baseline, 25% of patients in the placebo group and 12.5% of patients in the nerandomilast groups would initiate nintedanib after 26 weeks, resulting in an assumed effect of nerandomilast of 71 mL. The standard deviation was assumed to be 280 mL. Under the graphical testing procedure, it was estimated that a sample size of 1,008 patients (336 per treatment group) would have a power of 94% to detect a 71 mL between-group difference in the primary end point at a two-sided alpha level of 0.05.
Data management, patient withdrawals	Data management occurred in accordance with the Declaration of Helsinki, the ICH GCP guidelines, local regulations, and Boehringer's SOPs. In the primary endpoint analysis, missing data were not imputed except for missing values for change in FVC for patients who died before week 52, which were imputed based on the tenth percentile of observed values.
Key: bid, twice a day; ES, entered set; FAS, full analysis set; FVC, forced vital capacity; GCP, Good Clinical Practice; ICH, International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MMRM, mixed-effect model for repeated measures; PK, pharmacokinetic; PKS, pharmacokinetic parameter analysis set; REML, restricted maximum likelihood; RS, randomised set; SOP, standard operating procedure; TS, Treated Set. **Source:** FIBRONEER-IPF CTR[103]; FIBRONEER-ILD CTR[104]; Richeldi et al. 2025[28]; Maher et al. 2025.[100]	

2.5 Critical appraisal of the relevant clinical effectiveness evidence

Critical appraisal of FIBRONEER-IPF and FIBRONEER-ILD was conducted using the Cochrane Risk of Bias checklist, full details of which are provided in Appendix B.

The overall risk of bias is low with the FIBRONEER trial programme providing high-quality randomised controlled trial (RCT) evidence of the efficacy and safety of nerandomilast for the treatment of IPF and PPF. The monotherapy population of both trials provides data of direct relevance to the decision problem addressed in this submission. This population (the 'no AF background therapy' cohort) was a pre-

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specified subgroup and in both trials, randomisation was stratified by the presence of AF background therapy (yes vs no) (Appendix I). The nerandomilast 18 mg bid arm provides data for the intended starting dose of nerandomilast in the UK clinical practice and the nerandomilast 9 mg bid arm provides data for the intended reduced dose of nerandomilast if required.

While the FIBRONEER trials do not provide an active treatment comparison, the placebo arm can be considered representative of BSC and robust individual patient-level data (IPD) analyses are presented in Section 2.10 providing comparison of nerandomilast to active treatment (nintedanib). Outcomes measured in FIBRONEER-IPF and FIBRONEER-ILD are those of clinical relevance to patients and healthcare professionals and cover markers of disease progression and worsening (pulmonary function, physical function, exacerbations and hospitalisations) as well as mortality, safety and tolerability, and HRQL outcomes.

There are some differences in the concomitant immunosuppressant medication rules applied in the FIBRONEER-ILD trial compared with UK clinical practice and some minor differences in the baseline characteristics of patients in the FIBRONEER trials versus clinical practice that are discussed further in Section 2.13. However, the general consensus of clinical experts consulted is that the outcomes observed in the FIBRONEER trial programme are expected to translate to UK clinical practice.[81]

2.6 Clinical effectiveness results of the relevant studies

Data from the FIBRONEER trial programme are available from two database locks:

- DBL1 – main analysis performed after the last randomised patient had completed the Week 52 assessment (cut-off date of 16 August 2024 in FIBRONEER-IPF and 18 December 2024 in FIBRONEER-ILD)[28, 100]
- DBL2 – final analysis performed after the last patient had completed the trial (cut-off date [redacted] in FIBRONEER-IPF and [redacted] in FIBRONEER-ILD)[103, 104]

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An overview of the clinical effectiveness data available and where they are presented is summarised in Appendix I. In this section, data for the monotherapy population are presented up to DBL2 data to be as complete as possible, with the exception of data relating to the primary endpoint which is presented at the pre-specified timepoint of 52 Weeks. All p-values presented in this section, except those for the primary and key secondary endpoint in the FAS, should be considered exploratory in nature.

2.6.1 Change from baseline in forced vital capacity (mL)

2.6.1.1 FIBRONEER-IPF

The primary endpoint of FIBRONEER-IPF was met, with a statistically significant relative reduction in lung function decline of 37% ($p < 0.001$) at 52 weeks, as measured by the adjusted mean change from baseline in FVC versus placebo (−114.7 mL versus −183.5 mL) in the FAS (see Appendix K).[28]

In the monotherapy population, a clinically meaningful relative reduction in lung function decline of 47% at 52 weeks was observed, as measured by the adjusted mean change from baseline in FVC versus placebo (−79.2 mL versus −148.7 mL) (Figure 8).[28]

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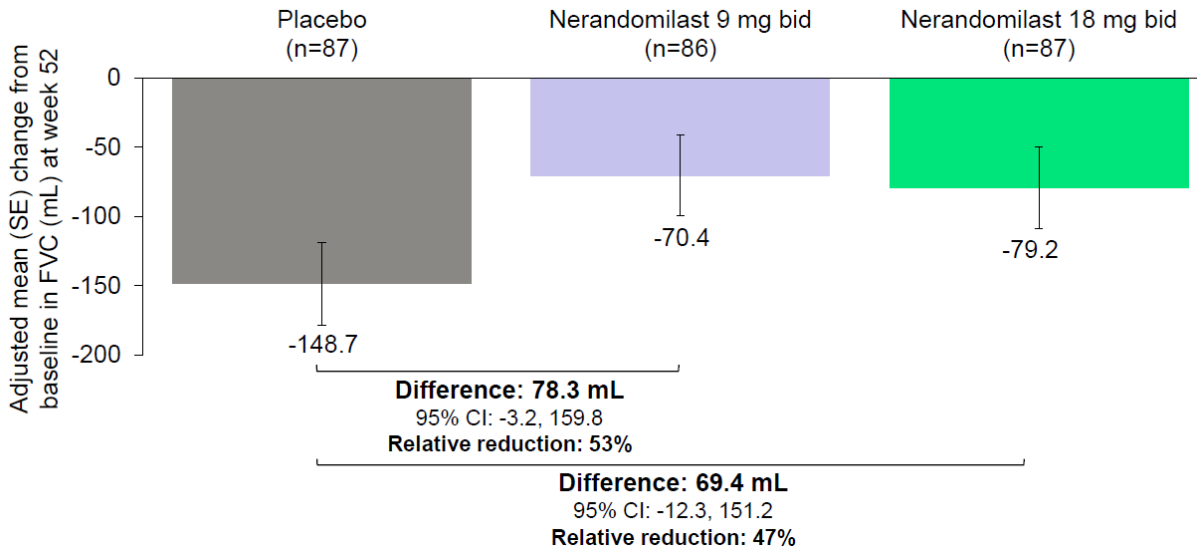
Figure 8: Change from baseline in FVC (mL) at Week 52, FIBRONEER-IPF ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; CI, confidence interval; FVC, forced vital capacity; SE, standard error.
Notes: Based on a mixed model for repeated measures, with fixed effects of treatment, baseline antifibrotic therapy and baseline FVC.
Source: Adapted from Richeldi et al. 2025.[28]

Nerandomilast 18 mg bid showed early onset and sustained treatment effect with a separation from the placebo group in the mean change from baseline in FVC (mL) as early as Week 2, which continued to diverge up to Week 88 (Figure 9).[105]

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Figure 9: Change from baseline in FVC (mL) up to DBL2, FIBRONEER-IPF ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; DBL2, database lock 2; FVC, forced vital capacity; nera, nerandomilast; SE, standard error.
Source: FIBRONEER-IPF CSAP (Figure 47.2.2.1.1.2).[105]

The adjusted annual rate of decline in FVC over 88 weeks was lower in the nerandomilast 18 mg bid group compared with placebo, at [redacted] versus [redacted] (Table 8).[105]

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Table 8: Annual rate of decline in FVC (mL/year) up to 88 weeks, FIBRONEER-IPF ('no AF background therapy' cohort)

	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo
Number of patients analysed	[redacted]	[redacted]	[redacted]
Adjusted rate of decline over 88 weeks (95% CI)	[redacted]	[redacted]	[redacted]
Adjusted rate difference vs placebo (95% CI)	[redacted]	[redacted]	[redacted]

Key: AF, antifibrotic; CI, confidence interval; FVC, forced vital capacity.
Notes: Based on a random coefficient regression, with fixed effects of treatment, baseline antifibrotic therapy and baseline FVC, and random effects for time and intercept for each patient. Within-patient errors are modelled by unstructured variance–covariance structure.
Source: FIBRONEER-IPF CSAP (Table 47.2.2.6.1).[105]

2.6.1.2 FIBRONEER-ILD

The primary endpoint of FIBRONEER-ILD was met, with a statistically significant relative reduction in lung function decline of 41% ($p < 0.001$) at 52 weeks, as measured by the adjusted mean change from baseline in FVC for nerandomilast 18 mg bid versus placebo (−98.6 mL versus −165.8 mL) in the FAS (Appendix L).[100]

In the monotherapy population, a clinically meaningful relative reduction in lung function decline of 38% at 52 weeks was observed, as measured by the adjusted mean change from baseline in FVC versus placebo (−95.2 mL versus −154.1 mL) (Figure 10).[100]

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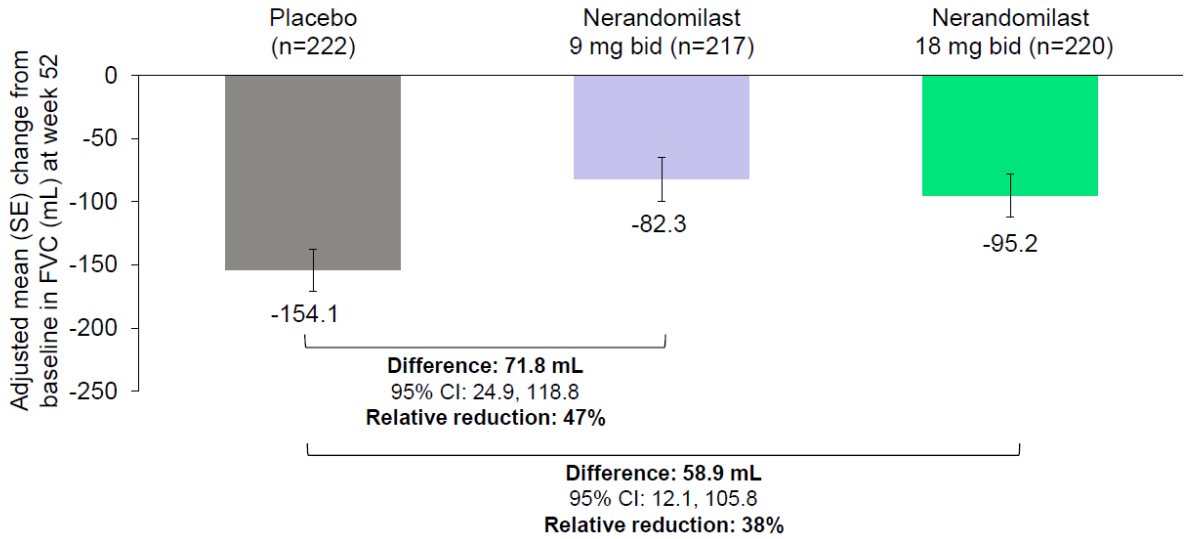
Figure 10: Change from baseline in FVC (mL) at Week 52, FIBRONEER-ILD ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; CI, confidence interval, HRCT, high-resolution computed tomography; FVC, forced vital capacity; SE, standard error.
Notes: Based on a mixed model for repeated measures, with fixed effects of treatment, baseline nintedanib therapy, baseline HRCT pattern and baseline FVC.
Source: Adapted from Maher et al. 2025.[100]

Mean change from baseline data up to DBL2 showed an improvement in lung function in the first 12 weeks of nerandomilast 18 mg bid use (Figure 11).[106] This is an unprecedented outcome in the treatment of pulmonary fibrosis where the goal is to stop the decline in lung function given the typically irreversible and chronic progressive nature of fibrosis.

The nerandomilast 18 mg bid group continued to diverge from the placebo group up to Week 88, presenting sustained benefit of nerandomilast.[106]

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Figure 11: Change from baseline in FVC (mL) over the duration of the trial (DBL2), FIBRONEER-ILD ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; DBL2, database lock 2; FVC, forced vital capacity; nera, nerandomilast; SE, standard error.
Source: FIBRONEER-ILD CSAP (Figure 69.2.3.1.1.2).[106]

The adjusted annual rate of decline in FVC over 52 weeks was lower in the nerandomilast 18 mg bid group compared with placebo at [redacted] versus [redacted] (Table 9).

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Table 9: Annual rate of decline in FVC (mL/year) over 52 weeks, FIBRONEER-ILD ('no AF background therapy' cohort)

	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo
Number of patients analysed	[redacted]	[redacted]	[redacted]
Adjusted rate of decline over 52 weeks (95% CI)	[redacted]	[redacted]	[redacted]
Adjusted rate difference vs placebo (95% CI)	[redacted]	[redacted]	[redacted]

Key: AF, antifibrotic; bid, twice a day; CI, confidence interval; HRCT, high-resolution computed tomography; FVC, forced vital capacity.
Notes: Based on a random coefficient regression, with fixed effects of treatment, baseline nintedanib therapy, baseline HRCT pattern and baseline FVC, and random effects for time and intercept for each patient.
Source: FIBRONEER-ILD CSAP-DBL1 (Table 34.2.3.1.2.1).[107]

2.6.2 Time to the first occurrence of acute idiopathic pulmonary fibrosis exacerbation, first hospitalisation for respiratory cause or death over the duration of the trial

2.6.2.1 FIBRONEER-IPF

The key secondary endpoint of FIBRONEER-IPF was not met, with no statistically significant difference in the composite endpoint of time to the first occurrence of acute IPF exacerbation, first hospitalisation for respiratory cause or death up to DBL1 in the FAS (p = 0.31) (see Appendix K).[28]

However, in the monotherapy population, a clinically meaningful benefit in favour of nerandomilast 18 mg bid was observed in the composite endpoint up to DBL2 with a [redacted] reduction in the risk of acute exacerbation, first hospitalisation for respiratory cause or death up to DBL2 (Figure 12).[105] Of the individual events of the key secondary endpoint, acute exacerbation occurred the most in the nerandomilast 18 mg bid group ([redacted]), whereas hospitalisations for respiratory causes was the most common in the placebo group ([redacted]) (Figure 12).[105]

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Figure 12: Time to first acute exacerbation, first hospitalisation for respiratory cause or death up to DBL2, FIBRONEER-IPF ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; CI, confidence interval; DBL2, database lock 2; IPF, idiopathic pulmonary fibrosis; nera, nerandomilast.
Notes: Based on cox proportional hazards model include treatment, baseline antifibrotic therapy, age, baseline FVC % predicted and baseline DL_{CO} predicted (corrected for haemoglobin as covariates.
Source: FIBRONEER-IPF CSAP (Figure 47.5.2.1).[105]

There was a nominally significant benefit in the time to death for nerandomilast 18 mg bid compared with placebo (HR:) of the individual components contributing to the key secondary endpoint (Figure 12). The cumulative incidence of time to death is shown in Figure 13.[105]

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Figure 13: Time to death up to DBL2, FIBRONEER-IPF ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; DBL2, database lock 2; nera, nerandomilast.
Source: FIBRONEER-IPF CSAP (Figure 47.2.1.2.1.5.2).[105]

2.6.2.2 FIBRONEER-ILD

In the FAS, while the risk of having a key secondary endpoint event was numerically lower in the nerandomilast 18 mg bid group compared with placebo (HR: 0.77; 95% CI: 0.59, 1.01), the key secondary endpoint of FIBRONEER-ILD was not met, with no statistically significant difference in the composite endpoint of time to the first occurrence of acute ILD exacerbation, first hospitalisation for respiratory cause or death up to DBL1 (p = 0.06) (see Appendix L).[100]

In the monotherapy population, a nominally significant benefit was observed in the composite endpoint up to DBL2 with a [redacted] reduction in the risk of acute exacerbation, first hospitalisation for respiratory cause or death (Figure 14).[106] Of the individual events of the key secondary endpoint, hospitalisations for respiratory causes was the most common event in the nerandomilast 18 mg bid group ([redacted]) and the placebo group ([redacted]) (Figure 14).[106]

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Figure 14: Time to first acute exacerbation, first hospitalisation for respiratory cause or death up to DBL2, FIBRONEER-ILD ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; CI, confidence interval; DBL2, database lock 2; ILD, interstitial lung disease; nera, nerandomilast.
Notes: Based on cox proportional hazards model include treatment, baseline nintedanib therapy, baseline HRCT pattern, age, baseline FVC % predicted and baseline DL_{CO} predicted (corrected for haemoglobin as covariates.
Source: FIBRONEER-ILD CSAP (Figure 69.4.2.1.1.1).[106]

There was also a nominally significant benefit on four out of five individual components contributing to the composite endpoint, for nerandomilast 18 mg bid versus placebo: time to first acute ILD exacerbation or death (HR, [redacted]), time to first hospitalisation for respiratory cause or death (HR, [redacted]), time to first hospitalisation for respiratory cause (HR, [redacted]) and time to death (HR, [redacted]; Figure 14), with the largest risk reduction in the latter endpoint. The cumulative incidence of time to death is shown in Figure 15.[106]

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Figure 15: Time to death up to DBL2, FIBRONEER-ILD ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; DBL2, database lock 2; nera, nerandomilast.
Source: FIBRONEER-ILD CSAP (Figure 69.2.2.2.2.5.3).[106]

2.6.3 Change from baseline in forced vital capacity % predicted and DL_{CO} % predicted

2.6.3.1 FIBRONEER-IPF

A numerical benefit in favour of nerandomilast 18 mg bid compared with placebo was observed in the adjusted mean change from baseline in FVC % predicted and DL_{CO} % predicted at Week 52, with a smaller change from baseline in FVC % predicted [redacted] and DL_{CO} % predicted [redacted] in the monotherapy population (Table 10).[105]

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Table 10: Change from baseline in FVC % predicted and DL_{CO} % predicted at Week 52, FIBRONEER-IPF ('no AF background therapy' cohort)

	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo
FVC % predicted			
N analysed	[redacted]	[redacted]	[redacted]
Adjusted mean (SE) change from baseline in FVC % of predicted value at Week 52	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)	[redacted]	[redacted]	[redacted]
DL_{CO} % of predicted value			
N analysed	[redacted]	[redacted]	[redacted]
Adjusted mean (SE) change from baseline in DL_{CO} % of predicted value at Week 52	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)	[redacted]	[redacted]	[redacted]

Key: AF, antifibrotic; bid, twice a day; CI, confidence interval; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; N, number; SE, standard error.
Notes: Adjusted analyses based on a mixed model for repeated measures, with fixed effects of treatment, baseline antifibrotic therapy and baseline FVC. p-values not adjusted for multiplicity and should be considered exploratory in nature.
Source: FIBRONEER-IPF CSAP (Table 47.2.2.1.2.1, Table 47.2.2.1.2.3, Table 47.2.2.1.3.1 and Table 47.2.2.1.3.3).[105]

Nerandomilast 18 mg bid showed early onset and sustained treatment effect with a separation from the placebo group in the mean change from baseline in the FVC % predicted as early as Week 2, which continued to diverge up to Week 88 (Figure 16).[105]

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Figure 16: Change from baseline in FVC % predicted up to DBL2, FIBRONEER-IPF ('no AF background therapy' cohort)



Key: bid, twice a day; DBL, database lock; FVC, forced vital capacity; nera, nerandomilast; SE, standard error.
Source: FIBRONEER-IPF CSAP (Figure 47.2.2.1.2.2).[105]

Table 11 presents the composite endpoints of absolute decline from baseline in FVC % predicted of > 10% or death and absolute decline from baseline in DL_{CO} % predicted of > 15% or death. These endpoints are representative of progression-free periods of living. Numerical benefit in favour of nerandomilast 18 mg bid was observed for both endpoints (Table 11).[105]

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Table 11: Time to absolute decline from baseline in FVC % predicted of > 10% or death and DL_{CO} % predicted of > 15% or death up to DBL2, FIBRONEER-IPF ('no AF background therapy' cohort)

	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo
Patients with an absolute decline from baseline in FVC % predicted of > 10% or death, n (%)	[redacted]	[redacted]	[redacted]
HR vs placebo (95% CI)	[redacted]	[redacted]	[redacted]
Absolute decline from baseline in DL_{CO} % predicted of > 15% or death	[redacted]	[redacted]	[redacted]
HR vs placebo (95% CI)	[redacted]	[redacted]	[redacted]

Key: AF, antifibrotic; CI, confidence interval; DBL2, database lock 2; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HR, hazard ratio.
Notes: Based on cox proportional hazards model include treatment, baseline antifibrotic therapy, age, baseline FVC % predicted and baseline DL_{CO} predicted (corrected for haemoglobin as covariates.
Source: FIBRONEER-IPF CSAP (Table 47.2.1.2.1.3.1 and Table 47.2.1.2.1.4.1).[105]

2.6.3.2 FIBRONEER-ILD

A numerical benefit in favour of nerandomilast 18 mg bid was observed compared with placebo in the adjusted mean change from baseline in FVC % predicted at Week 52, with a smaller change from baseline in FVC % predicted [redacted] (Table 12) in the monotherapy population.[106] Conversely, the adjusted mean change from baseline in DL_{CO} % predicted was slightly larger in the nerandomilast 18 mg bid group compared with placebo [redacted] (Table 12).[106]

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Table 12: Changes from baseline in FVC % predicted and DL_{CO} % predicted at Week 52, FIBRONEER-ILD ('no AF background therapy' cohort)

	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo
FVC % predicted			
N analysed	[redacted]	[redacted]	[redacted]
Adjusted mean (SE) change from baseline in FVC % of predicted value at Week 52	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)	[redacted]	[redacted]	[redacted]
DL_{CO} % predicted			
N analysed	[redacted]	[redacted]	[redacted]
Adjusted mean (SE) change from baseline in DL_{CO} % of predicted value at Week 52	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)	[redacted]	[redacted]	[redacted]

Key: bid, twice a day; CI, confidence interval; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; N, number; SE, standard error.
Notes: Adjusted analyses based on a mixed model for repeated measures, with fixed effects of treatment, baseline nintedanib therapy, baseline HRCT pattern and baseline FVC. p-values not adjusted for multiplicity and should be considered exploratory in nature.
Source: FIBRONEER-ILD CSAP (Table 69.2.3.1.3.1, Table 69.2.3.1.3.3, Table 69.2.3.1.4.1 and Table 69.2.3.1.4.3).[106]

Early onset of treatment effect was observed with nerandomilast 18 mg bid, with an improvement in FVC % predicted from baseline at Week 2 that was maintained through to Week 12 (Figure 17).[106] The nerandomilast 18 mg bid group continued to diverge from the placebo group up to Week 88, presenting sustained benefit of nerandomilast.[106]

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Figure 17: Change from baseline in FVC % predicted up to DBL2, FIBRONEER-ILD ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; DBL2, database lock 2; FVC, forced vital capacity; nera, nerandomilast; pred, predicted; SE, standard error.
Source: FIBRONEER-ILD CSAP (Figure 69.2.3.1.3.2).[106]

Table 13 presents the composite endpoints of absolute decline from baseline in FVC % predicted of > 10% or death and absolute decline from baseline in DL_{CO} % predicted of > 15% or death. Numerical benefit in favour of nerandomilast 18 mg bid was observed for both endpoints (Table 13) in the monotherapy population.[106]

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Table 13: Time to absolute decline from baseline in FVC % predicted of > 10% or death and DL_{CO} % predicted of > 15% or death up to DBL2, FIBRONEER-ILD ('no AF background therapy' cohort)

	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo
Patients with an absolute decline from baseline in FVC % predicted of > 10% or death, n (%)	[redacted]	[redacted]	[redacted]
HR vs placebo (95% CI)	[redacted]	[redacted]	[redacted]
Absolute decline from baseline in DL_{CO} % predicted of > 15% or death	[redacted]	[redacted]	[redacted]
HR vs placebo (95% CI)	[redacted]	[redacted]	[redacted]

Key: bid, twice a day; CI, confidence interval; DBL2, database lock 2; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HR, hazard ratio; HRCT, high-resolution computed tomography.
Notes: Based on cox proportional hazards model include treatment, baseline nintedanib therapy, baseline HRCT pattern, age, baseline FVC % predicted and baseline DL_{CO} predicted (corrected for haemoglobin as covariates.
Source: FIBRONEER-ILD CSAP (Tables 69.2.2.2.2.3.1 and 69.2.2.2.2.4.1).[106]

2.6.4 Change from baseline in Living with Pulmonary Fibrosis questionnaire symptoms

Patient quality of life was assessed using the Living with Pulmonary Fibrosis (L-PF) questionnaire. The L-PF questionnaire is a self-administered, 44-item questionnaire that focuses on patient symptoms (dyspnoea, cough and fatigue) and the impact of these symptoms on patients. The questionnaire's summary scores range from 0 to 100, with the higher score indicating greater impairment.[103, 104]

2.6.4.1 FIBRONEER-IPF

The adjusted mean (SE) change from baseline in the L-PF Impact total score at Week 52 was [redacted] in the nerandomilast 18 mg bid arm of the monotherapy population versus [redacted] in the placebo arm [redacted].[105]

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The adjusted mean (SE) change from baseline in the L-PF symptom total score at Week 52 was [redacted] in the nerandomilast 18 mg bid arm of the monotherapy population versus [redacted] in the placebo arm [redacted].[105]

Adjusted mean (SE) changes from baseline in specific symptom scores are presented in Table 14. Time to the deterioration in L-PF symptoms (dyspnoea and cough) or death up to DBL2 analyses showed a numerical benefit in favour of nerandomilast 18 mg bid compared with placebo (Table 14).[105]

Table 14: L-PF symptom scores at Week 52 and time to the deterioration in L-PF symptoms (dyspnoea or cough) or death up to DBL2, FIBRONEER-IPF ('no AF background therapy' cohort)

	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo
L-PF Symptoms Dyspnoea score – adjusted mean CFB (SE)	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)	[redacted]	[redacted]	[redacted]
L-PF Symptoms Cough score – adjusted mean CFB (SE)	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)	[redacted]	[redacted]	[redacted]
L-PF Symptoms Fatigue score – adjusted mean CFB (SE)	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)	[redacted]	[redacted]	[redacted]
L-PF Symptoms Dyspnoea deterioration or death, n (%)	[redacted]	[redacted]	[redacted]
HR vs placebo* (95% CI)	[redacted]	[redacted]	[redacted]
L-PF Symptoms Cough deterioration or death, n (%)	[redacted]	[redacted]	[redacted]
HR vs placebo* (95% CI)	[redacted]	[redacted]	[redacted]

Key: AF, antifibrotic; bid, twice a day; CI, confidence interval; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; HR, hazard ratio; IPF, Idiopathic pulmonary fibrosis; L-PF, Living with Pulmonary Fibrosis questionnaire.

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	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo
Notes: Based on a mixed model for repeated measures, with fixed effects of treatment, baseline antifibrotic therapy and baseline score. Dyspnoea deterioration defined as absolute increase in dyspnoea score > 9; cough deterioration defined as absolute increase in cough score > 16. **Source:** FIBRONEER-IPF CSAP (Table 47.2.2.2.3.3, Table 47.2.2.2.3.5, Table 47.2.2.2.3.7, Table 47.2.2.3.10.1 and Table 47.2.2.3.11.1).[105]			

2.6.4.2 FIBRONEER-ILD

The adjusted mean (SE) change from baseline in the L-PF Impact total score at Week 52 was [redacted] in the nerandomilast 18 mg bid arm of the monotherapy population versus [redacted] in the placebo arm (difference: [redacted]).[106]

The adjusted mean (SE) change from baseline in the L-PF symptom total score at Week 52 was [redacted] in the nerandomilast 18 mg bid arm of the monotherapy population versus [redacted] in the placebo arm (difference: [redacted]).[106]

Adjusted mean (SE) changes from baseline in specific symptom scores are presented in Table 15. Time to the deterioration in L-PF symptoms (dyspnoea, cough and fatigue) or death up to DBL2 analyses showed a numerical benefit in favour of nerandomilast 18 mg bid compared with placebo (Table 15).[106]

Table 15: L-PF symptom scores at Week 52 and time to the deterioration in L-PF symptoms (dyspnoea, cough or fatigue) or death up to DBL2, FIBRONEER-ILD ('no AF background therapy' cohort)

	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo
L-PF Symptoms Dyspnoea score – adjusted mean CFB (SE)	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)	[redacted]	[redacted]	[redacted]
L-PF Symptoms Cough score – adjusted mean CFB (SE)	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)	[redacted]	[redacted]	[redacted]

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	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo
L-PF Symptoms Fatigue score – adjusted mean CFB (SE)	[redacted]	[redacted]	[redacted]
Difference vs placebo (95% CI)	[redacted]	[redacted]	[redacted]
L-PF symptoms dyspnoea deterioration or death, n (%)	[redacted]	[redacted]	[redacted]
HR vs placebo* (95% CI)	[redacted]	[redacted]	[redacted]
L-PF symptoms cough deterioration or death, n (%)	[redacted]	[redacted]	[redacted]
HR vs placebo* (95% CI)	[redacted]	[redacted]	[redacted]
L-PF symptoms fatigue deterioration or death, n (%)	[redacted]	[redacted]	[redacted]
HR vs placebo* (95% CI)	[redacted]	[redacted]	[redacted]

Key: AF, antifibrotic; bid, twice a day; CI, confidence interval; HR, hazard ratio; HRCT, high-resolution computed tomography; L-PF, Living with Pulmonary Fibrosis questionnaire.
Notes: Based on a mixed model for repeated measures, with fixed effects of treatment, baseline nintedanib therapy, baseline HRCT pattern and baseline score. Dyspnoea deterioration defined as absolute increase in dyspnoea score > 9; cough deterioration defined as absolute increase in cough score > 16; fatigue deterioration defined as absolute increase in fatigue score > 13.
Source: FIBRONEER-ILD CSAP (Table 69.2.3.3.11.1, Table 69.2.3.3.12.1 and Table 69.2.3.3.13.1).[106]

2.6.5 Change from baseline in EQ-5D-5L questionnaire

Distribution of change from baseline in EQ-5D visual analogue scale by study visit is shown for the monotherapy population of FIBRONEER-IPF and FIBRONEER-ILD in Figure 18 and Figure 19, respectively. No meaningful difference was observed in EQ-5D questionnaire outcomes over time; changes observed at later visits are highly varied due to small patient numbers at risk and do not reflect a population level change.

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Figure 18: Change from baseline in EQ-5D VAS up to DBL2, FIBRONEER-IPF ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; CFB, change from baseline; DBL2, database lock 2; nera, nerandomilast; SE, standard error; VAS, visual analogue scale.
Notes: The error bar shows mean +/- SE values.
Source: FIBRONEER-IPF EQ-5D data on file.[108]

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Figure 19: Change from baseline in EQ-5D VAS up to DBL2, FIBRONEER-ILD ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; CFB, change from baseline; DBL2, database lock 2; nera, nerandomilast; SE, standard error; VAS, visual analogue scale.
Notes: The error bar shows mean +/- SE values.
Source: FIBRONEER-ILD EQ-5D data on file.[109]

2.6.6 Use of supplemental oxygen

2.6.6.1 FIBRONEER-IPF

At baseline, a total of [redacted] patients in the nerandomilast 18 mg bid treatment arm and [redacted] patients in the placebo arm of the monotherapy population were not using supplemental oxygen according to patients' response to the "*Do you use supplemental oxygen*?" question in the L-PF questionnaire.[105]

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Over the whole trial (up to DBL2), [redacted] patients in the nerandomilast 18 mg bid arm [redacted] started use of supplemental oxygen compared with [redacted] patients in the placebo arm [redacted].[105] This represents a clinically meaningful reduction in the use of supplemental oxygen, according to clinical experts.[81]

The estimated cumulative incidence for time to first use of supplemental oxygen is shown in Figure 20.

Figure 20: Estimated cumulative incidence for time to first use of supplemental oxygen up to DBL2, FIBRONEER-IPF ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; DBL2, database lock 2; nera, nerandomilast.
Source: FIBRONEER-IPF CSAP (Figure 47.2.2.3.9.2).[105]

2.6.6.2 FIBRONEER-ILD

At baseline, a total of [redacted] patients in the nerandomilast 18 mg bid treatment arm and [redacted] patients in the placebo arm of the monotherapy population were not using supplemental oxygen according to patients' response to the "*Do you use supplemental oxygen*?" question in the L-PF questionnaire.[106]

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Over the whole trial (up to DBL2), [redacted] patients in the nerandomilast 18 mg bid arm ([redacted]) started using supplemental oxygen compared with [redacted] patients in the placebo arm [redacted].[106] This represents a clinically meaningful reduction in the use of supplemental oxygen, according to clinical experts.[81]

The estimated cumulative incidence for time to first use of supplemental oxygen is shown in Figure 21.

Figure 21: Estimated cumulative incidence function for time to first use of supplemental oxygen up to DBL2, FIBRONEER-ILD ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; DBL2, database lock 2; nera, nerandomilast.
Source: FIBRONEER-ILD CSAP (Figure 69.2.3.3.10.3)[106]

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2.7 Subsequent treatments used in the relevant studies

2.7.1 FIBRONEER-IPF

Subsequent treatment use was minimal and no single treatment was initiated in more than [redacted] in the monotherapy population for any treatment arm.[110] Treatments that were initiated were mainly focused to symptom management. In the nerandomilast 18 mg bid arm of the monotherapy population, the only treatment initiated in more than [redacted] was prednisolone.[110] [redacted] received nintedanib or pirfenidone therapy following discontinuation of nerandomilast 18 mg bid treatment; [redacted] received nintedanib following discontinuation of nerandomilast 9 mg bid treatment. In the placebo arm of the monotherapy population, [redacted] received nintedanib after stopping trial treatment and one patient received pirfenidone.[110]

2.7.2 FIBRONEER-ILD

Subsequent treatment use was minimal and [redacted] in the monotherapy population for any treatment arm.[111] Treatments that were initiated were mainly focused on managing symptoms. In the nerandomilast 18 mg bid arm of the monotherapy population, [redacted] received subsequent nintedanib therapy and [redacted] received subsequent pirfenidone therapy. A [redacted] in the nerandomilast 9 mg bid arm and [redacted] patients in the placebo arm received subsequent nintedanib therapy and [redacted] patients in the placebo arm received subsequent pirfenidone therapy.[111]

2.8 Subgroup analysis

Please see Appendix C for pre-specified subgroup analyses in the FAS population of FIBRONEER-IPF and FIBRONEER-ILD.

2.9 Meta-analysis

Results for pooled IPD analyses of FIBRONEER-IPF and FIBRONEER-ILD in the monotherapy population are presented below.

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Compared with placebo, nerandomilast 18 mg bid monotherapy was shown to significantly[101]:

- Slow disease progression, with an adjusted mean difference in change from baseline to Week 52 in FVC of [redacted] (95% CI: [redacted]), representing a [redacted] relative reduction in lung function decline ([redacted] versus [redacted])
  - Early onset and sustained treatment effect was observed with a separation from the placebo group in the mean change from baseline in FVC (mL) as early as Week 2, which continued to diverge up to Week 88 (Figure 22)
- Reduce the risk of time to the first occurrence of acute exacerbation, first hospitalisation for respiratory cause or death versus placebo: [redacted] ([redacted])
- Reduce the risk of first acute exacerbation or death versus placebo: [redacted] ([redacted])
- Reduce the risk of hospitalisation for respiratory cause or death versus placebo: [redacted] ([redacted])
- Reduce the risk of death versus placebo: [redacted] (Figure 23 (Figure 24)
- Extend the periods of progression-free living, reducing the risk of time to FVC % predicted decline of > 10% or death versus placebo: [redacted] (Figure 25)

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Figure 22: Adjusted mean (SE) of absolute change from baseline in FVC (mL) up to 88 weeks, FIBRONEER-IPF and FIBRONEER-ILD pooled ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; FVC, forced vital capacity; nera, nerandomilast; SE, standard error.
Source: FIBRONEER-IPF and -ILD pooled analyses CSAP (Figure 85.1.2.1.1.2).[101]

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Figure 23: Time to first acute exacerbation, first hospitalisation for respiratory cause or death up to DBL2, FIBRONEER-IPF and FIBRONEER-ILD pooled ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; CI, confidence interval; DBL2, database lock 2; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; nera, nerandomilast.
Note: If fewer than 10 patients within the subgroup experienced an event, then estimate and CIs were not plotted.
Source: FIBRONEER-IPF and -ILD pooled analyses CSAP (85.1.2.2.3.1.7.1).[101]

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Figure 24: Time to death up to DBL2, FIBRONEER-IPF and FIBRONEER-ILD pooled ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; DBL2, database lock 2; nera, nerandomilast.
Source: FIBRONEER-IPF and -ILD pooled analyses CSAP (Figure 85.1.2.2.3.1.3.2).[101]

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Figure 25: Time to first absolute decline from baseline in FVC % predicted of > 10% or death up to DBL2, FIBRONEER-IPF and FIBRONEER-ILD pooled ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; DBL2, database lock 2; nera, nerandomilast.
Source: FIBRONEER-IPF and -ILD pooled analyses CSAP (Figure 85.1.2.2.3.1.4.2).[101]

2.10 Indirect and mixed treatment comparisons

2.10.1 Identification of comparator trials

As described in Appendix B, an SLR was conducted to identify relevant clinical evidence of the efficacy and safety of treatments for patients with IPF and PPF.

Access to the IPD for both the nerandomilast (FIBRONEER-IPF and FIBRONEER-ILD) and nintedanib (INPULSIS 1 and 2 [IPF] and INBUILD [PPF]) Phase III RCTs is a unique advantage of this appraisal, which enabled IPD-based methods for indirect treatment comparison (ITC) of nerandomilast versus nintedanib in both IPF and PPF. The INPULSIS and INBUILD trials are described in detail in Appendix B.

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Five additional trials investigating pirfenidone or nintedanib therapy (ASCEND, CAPACITY 1, CAPACITY 2, JAPICCTI-050121 and TOMORROW trials) for the treatment of IPF were considered feasible for inclusion in aggregate data-based ITC of nerandomilast versus nintedanib and nerandomilast versus pirfenidone. See Appendix B for a summary of these trials. As nintedanib is the only relevant comparator in PPF and robust IPD-based methods for ITC were possible, no aggregate data-based ITCs were considered for PPF. This aligns with NICE guidance that preferences IPD-based analyses where possible as the higher standard of ITC methodology.[112]

2.10.2 Feasibility assessment and baseline characteristics

Feasibility assessment was conducted to confirm network connections based on data availability for outcomes and populations of interest and the validity of networks in terms of similarity of trials with regard to study design and patient characteristics. Full details of the feasibility assessment for IPF aggregate data-based ITC are provided in the feasibility assessment report provided in the reference pack.[113] Feasibility assessment for PPF only included FIBRONEER-IPF and INBUILD for which IPD are available for all outcomes and populations of interest, and trials are similar with regard to study design and patient characteristics.

Baseline characteristics of patients enrolled to the INPULSIS trial programme (INPULSIS-1 and INPUSLIS-2 pooled data) are presented alongside those of patients enrolled to FIBRONEER-IPF in Table 16. Some differences are observed in baseline DL_{CO} % predicted, baseline FVC % predicted and time from diagnosis – all of which were adjusted for within the IPD-based ITC (Table 18).

Baseline characteristics of patients enrolled to the INBUILD trial are presented alongside those of patients enrolled to FIBRONEER-ILD in Table 17. Some differences are observed in baseline DL_{CO} % predicted, baseline FVC % predicted, time from diagnosis and prior use of immunomodulators – all of which were adjusted for within the IPD-based ITC (Table 18).

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Baseline characteristics of patients enrolled to other trials included in the aggregate data NMA for IPF are provided in the feasibility assessment report provided in the reference pack.[113] Notable differences were observed between FIBRONEER-IPF and comparator trials in time from diagnosis and geographical region, and some further differences were observed in FVC % predicted, DL_{CO} % predicted and supplemental oxygen use. Of these characteristics, FVC % predicted and DL_{CO} % predicted are considered prognostic factors and effect modifiers and time from diagnosis and supplemental oxygen use are considered prognostic factors (Table 18).

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Table 16: Baseline characteristics in FIBRONEER-IPF ('no AF background therapy cohort') and INPULSIS (IPF)

		FIBRONEER-IPF			INPULSIS	
Variable	**Level**	**NERA 18 mg bid (N = 87)**	**NERA 9 mg bid (N = 88)**	**Placebo -FIB (N = 87)**	**NDB 150 mg bid (N = 638)**	**Placebo-INP (N = 423)**
Age, years	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex (%)	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region (%)	Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ROW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status (%)	Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Former	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline weight, kg	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline DL_{CO}, % pred	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline FVC, % pred	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline FVC, mL	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis (%)	<6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≥6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supplemental oxygen use (%)	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: bid, twice a day; DL_{CO} % pred, diffusing capacity of the lungs for carbon monoxide percent predicted; FVC, forced vital capacity; FVC % pred= forced vital capacity percent predicted; NA, not available; NERA, nerandomilast; NDB, nintedanib; ROW, rest of the world; SD, standard deviation.
Source: Technical report for IPD meta-regression.[102]

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Table 17: Baseline characteristics in FIBRONEER-ILD ('no AF background therapy cohort') and INBUILD (PPF)

		FIBRONEER-ILD			INBUILD	
Variable	**Level**	**NERA 18 mg bid (N = 220)**	**NERA 9 mg bid (N = 220)**	**Placebo-FIB (N = 222)**	**NDB 150 mg bid (N = 663)**	**Placebo-INB (N = 332)**
Age, years	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex (%)	Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region (%)	Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ROW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (%)	American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status (%)	Never	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Former	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline weight	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline DL_{CO}, % pred	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline FVC, % pred	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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		FIBRONEER-ILD			INBUILD	
Variable	**Level**	**NERA 18 mg bid (N = 220)**	**NERA 9 mg bid (N = 220)**	**Placebo-FIB (N = 222)**	**NDB 150 mg bid (N = 663)**	**Placebo-INB (N = 332)**
Baseline FVC, mL	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis (%)	<6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	>=6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supplemental oxygen use (%)	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ILD diagnosis (%)	Autoimmune ILD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Hypersensitivity pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Idiopathic non-specific interstitial pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other ILDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Unclassifiable idiopathic interstitial pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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		FIBRONEER-ILD			INBUILD	
Variable	**Level**	**NERA 18 mg bid (N = 220)**	**NERA 9 mg bid (N = 220)**	**Placebo-FIB (N = 222)**	**NDB 150 mg bid (N = 663)**	**Placebo-INB (N = 332)**
Prior immunomodulators (%)	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior HD steroids (%)	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HRCT2 (%)	Other fibrotic patterns	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	UIP-like pattern	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCI category >3 (%)	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: bid, twice a day; CCI, Charlson comorbidity index; DL_{CO} % pred, diffusing capacity of the lungs for carbon monoxide percent predicted; FVC, forced vital capacity; FVC % pred, forced vital capacity percent predicted; HD, high dose; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; NA, not available; NERA, nerandomilast; NDB, nintedanib; ROW, rest of the world; SD, standard deviation; UIP, usual interstitial pneumonia.
Source: Technical report for IPD meta-regression.[102]

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2.10.3 Network and methodology

The following approaches to ITC were explored, including both methods using IPD (IPF and PPF) and aggregate data (IPF only):

- IPD meta-regression
- Bucher pairwise comparisons
- Bayesian network meta-analysis (NMA)

Of these methods, the IPD meta-regression is considered the most robust. As such, outcomes from this method are the focus of this section and used in the subsequent economic modelling. Key benefits of IPD meta-regression include the ability to standardise outcome definitions and measurement scales across studies and to apply a consistent statistical model to all included datasets.[114] The other important benefit is to enable researchers to explore and adjust for confounders and treatment effect modification arising from differences in study design or participant characteristics (see Section 2.10.2). By modelling within-study interactions at the participant level rather than cross-study interactions at the study level, IPD meta-regression reduces aggregation bias thereby enabling a more reliable assessment of effect modification and heterogeneity.

Aggregate data-based ITC methods are briefly described in this section with results provide in Appendix B.

2.10.3.1 Individual patient-level data meta-regression

The network diagram for IPD meta-regression for IPF and PPF is presented in Figure 26.[102] The selection of variables for inclusion in the IPD meta-regression model is based on the identification of potential effect modifiers and prognostic factors (confounders). These were identified based on published subgroup analyses and NMA, HTA submissions, previously conducted feasibility assessments and feedback from clinical experts, and are presented in Table 18.

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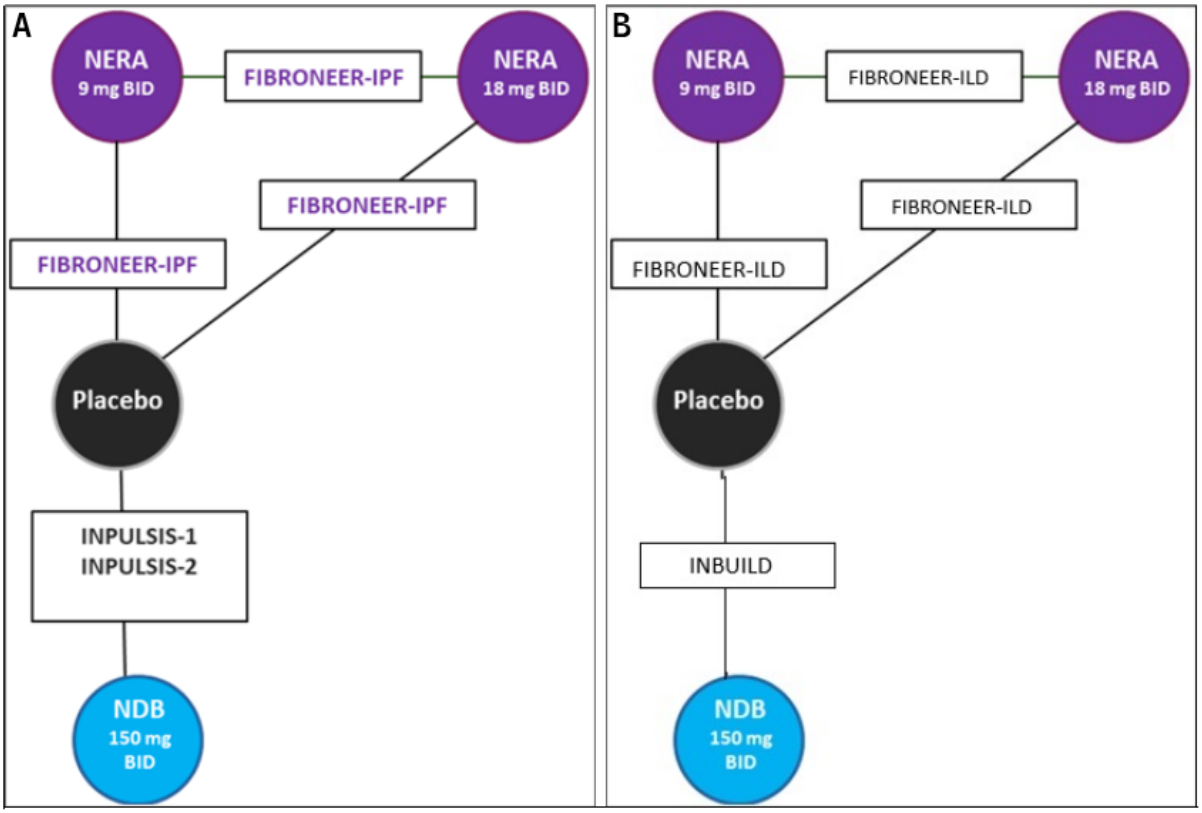
All variables were centred to the overall mean values from the combined FIBRONEER and INPUSIS/INBUILD trials. Study (FIBRONEER versus INPULSIS/INBUILD) was included in the model as a fixed effect, with FIBRONEER-IPF and FIBRONEER-ILD set as the reference categories for IPF and PPF, respectively.

Figure 26: Network diagrams for IPD meta-regression for (A) IPF and (B) PPF



Key: BID, twice a day; DBL2, database lock 2; ILD, interstitial lung disease; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib; NERA, nerandomilast; PPF, progressive pulmonary fibrosis.
Notes: IPD meta-regression used DBL2 data from all trials.
Source: Technical report for IPD meta-regression.[102]

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Table 18: Effect modifiers and prognostic factors included in the regression equations

Variable	IPF		PPF	
	Prognostic Variable	**Effect Modifier**	**Prognostic Variable**	**Effect Modifier**
Age (years)	✓	–	✓	–
FVC percent predicted	✓	✓	✓	✓
DL_{CO} percent predicted	✓	✓	✓	✓
Gender	✓	–	✓	–
Smoking status	✓	–	✓	–
Weight (kg)	✓	✓	✓	✓
Time since diagnosis (years)	✓	–	✓	–
Region	✓	–	✓	–
Supplemental oxygen use	✓	–	✓	–
Charlson comorbidity index (CCI)	✓	✓	✓	✓
Race	–	–	✓	–
HRCT pattern	–	–	✓	–
ILD diagnosis	–	–	✓	–
Prior use of Immunomodulators	–	–	✓	–
Prior use of High dose steroids	–	–	✓	–

Key: DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis, PPF, progressive pulmonary fibrosis.
Source: Technical Report for IPD meta-regression.[102]

IPD meta-regression can be implemented using either a one-stage or two-stage approach.[114] A one-stage approach was selected for this analyses (versus a two-stage approach) because it allows all studies and participant data to be modelled within a unified framework. This approach facilitates information-sharing across studies and provides a clearer understanding of between-study heterogeneity. It is particularly advantageous when one or more studies include a limited number of patients or events[114] – for example, FIBRONEER-IPF, which reports a small number of acute exacerbation events.

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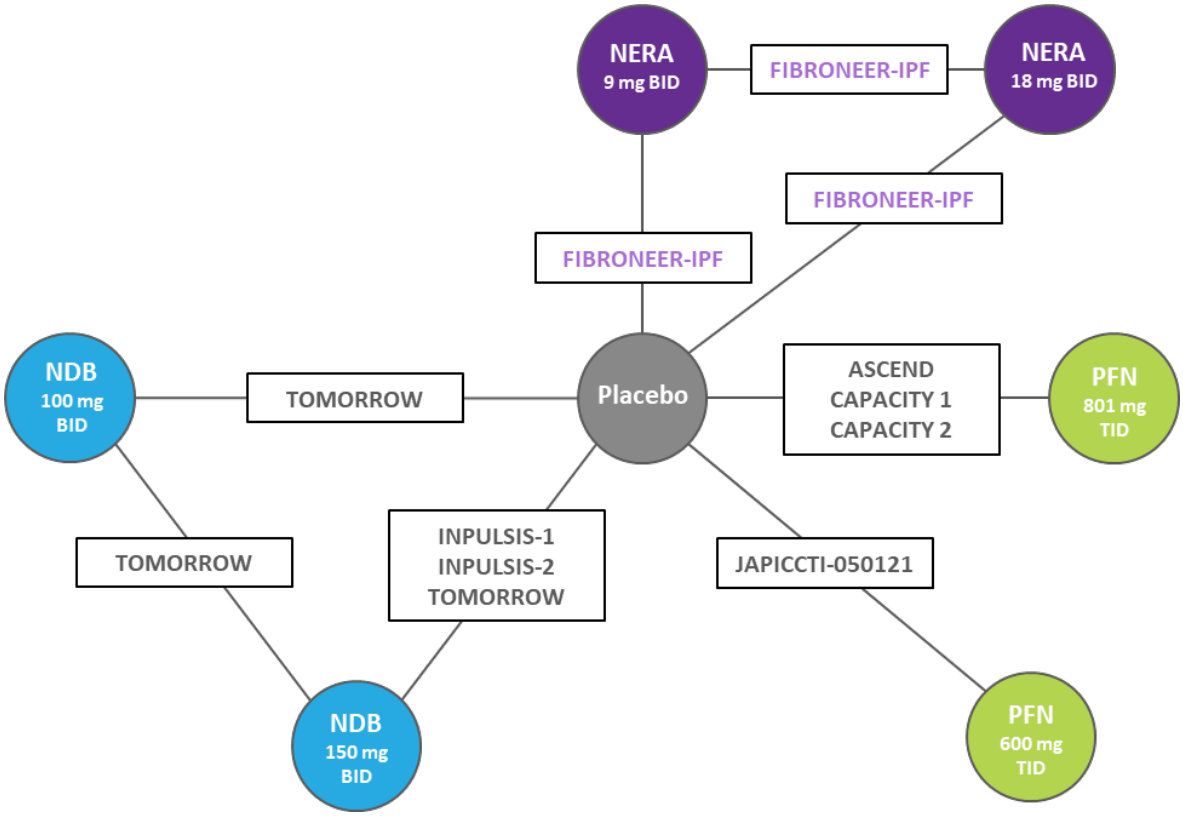
Full details of the IPD meta-regression methods and outcomes are provided in the IPD meta-regression technical report.[102] Key results for nerandomilast 18 mg bid versus nintedanib 150 mg bid are reported in Section 2.10.4.

2.10.3.2 Aggregate data indirect treatment comparisons

Patient-level data were not available for pirfenidone, so only unadjusted aggregate data-based ITC using published RCT data was possible (Bucher pairwise comparisons and Bayesian NMA). A network diagram is presented in Figure 27. Full details of the Bucher pairwise comparisons and Bayesian NMA are provided in the aggregate data-based ITC technical report provided in the reference pack.[115]

Figure 27: Network diagram for Bayesian NMA (IPF)



Key: BID, twice a day; NDB, nintedanib; NERA, nerandomilast; PFN, pirfenidone.
Source: ITC feasibility assessment report.[113]

Due to differences in baseline characteristics between FIBRONEER and comparator trials, including in characteristics known to be treatment effect modifiers, the unadjusted ITC results are likely confounded and should be interpreted with caution.

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Nintedanib and pirfenidone are viewed by clinical experts as having broadly similar efficacy for the treatment of IPF[93, 116] as demonstrated in independently published ITCs.[117, 118] A conclusion of comparative effectiveness for current AF therapies was also accepted by the NICE Committee in TA379 stating that *"[the committee] considered the effectiveness of nintedanib and discussed the results of the company NMA and concluded that the clinical effectiveness of nintedanib is similar to pirfenidone".*[18] It is therefore considered appropriate to apply IPD meta-regression outcomes for nerandomilast versus nintedanib to the comparison of nerandomilast versus pirfenidone.

2.10.4 Individual patient-level data meta-regression results

The relative effects of nerandomilast 18 mg bid versus nintedanib 150 mg bid in IPF and PPF derived from IPD meta-regression are presented for clinical efficacy outcomes in Table 19. Please see Section 2.11.3 for safety outcomes.

Nerandomilast 18 mg bid showed a clinically meaningfully lower risk of mortality compared with nintedanib 150 mg bid in both IPF (HR: [redacted]) and PPF (HR: [redacted];

Figure 28); and a numerically lower risk of acute exacerbation in PPF (HR: [redacted]; Figure 29).

Nerandomilast 18 mg bid showed similar effectiveness to nintedanib 150 mg bid in terms of disease progression as measured by lung function decline, with some FVC based outcomes numerically in favour of nerandomilast (slightly) and others numerically in favour of nintedanib (slightly), with no clinically meaningful differences observed (Table 19; Figure 30 to Figure 32).

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Table 19: Overview of key results from IPD meta-regression for nerandomilast 18 mg bid versus nintedanib 150 mg bid

Nerandomilast 18 mg bid vs nintedanib 150 mg	IPF	PPF
Time to event over the whole trial duration, hazard ratio (95% CI)		
Time to death	[redacted]*	[redacted]*
Time to first acute exacerbation	[redacted]	[redacted]*
Time to first ≥10% FVC % predicted decline	[redacted]	[redacted]
Time to respiratory related death	[redacted]*	[redacted]*
Absolute change from baseline at 52 weeks, mean difference (95% CI)		
FVC (mL)	[redacted]*	[redacted]*
FVC % predicted	[redacted]*	[redacted]*
Rate over the whole trial duration, relative rate (95% CI)		
Rate of progression	[redacted]	[redacted]

Key: bid, twice a day; CI, confidence interval; FVC, forced vital capacity; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.
Notes: *Indicates numerical benefit in favour of nerandomilast.
Source: Technical Report for IPD meta-regression.[102]

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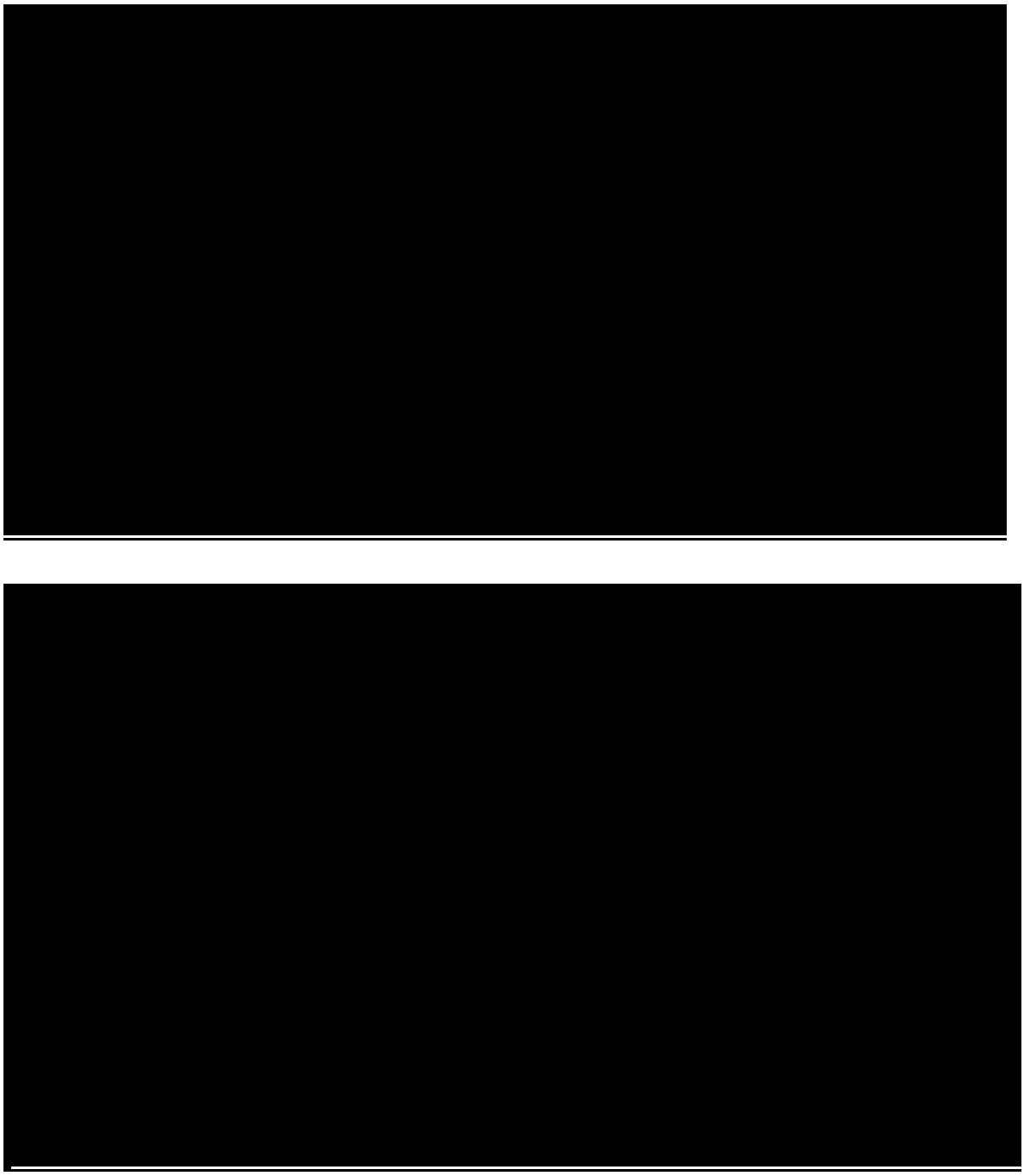
Figure 28: IPD meta-regression: time to mortality over the whole trial duration for nerandomilast and nintedanib in IPF (top panel) and PPF (bottom panel)



Key: bid, twice a day; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib; NERA, nerandomilast; PPF, progressive pulmonary fibrosis.
Notes: IPF analyses based on 50 events among 500 patients in the placebo group, 48 events among 638 patients in the NDB 150 mg bid group, 3 events among 87 patients in the NERA 18 mg bid group, and six events in the NERA 9 mg bid group. PPF analyses based on 81 events observed among 553 patients in the placebo group, 36 events among 332 patients in the NDB 150 mg bid group, 15 events among 220 patients in the NERA 18 mg bid group, and 22 events among 220 patients in the NERA 9 mg bid group.
Source: Technical report for IPD meta-regression.[102]

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Figure 29: IPD meta-regression: time to first acute exacerbation over the whole trial duration for nerandomilast and nintedanib in IPF (top panel) and PPF (bottom panel)





Key: bid, twice a day; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib; NERA, nerandomilast; PPF, progressive pulmonary fibrosis.
Notes: IPF analyses based on 47 events among 510 patients in the placebo group, 34 events among 638 patients in the NDB 150 mg bid group, 11 events among 87 patients in the NERA 18 mg bid group and three events among 88 patients in the NERA 9 mg bid group. PPF analyses based on 83 events among 553 patients in the placebo group, 36 events among 332 patients in the NBD 150 mg bid group, 18 events among 220 patients in the NERA 18 mg bid group and 25 events among 220 patients in the NERA 9 mg bid group.
Source: Technical report for IPD meta-regression.[102]

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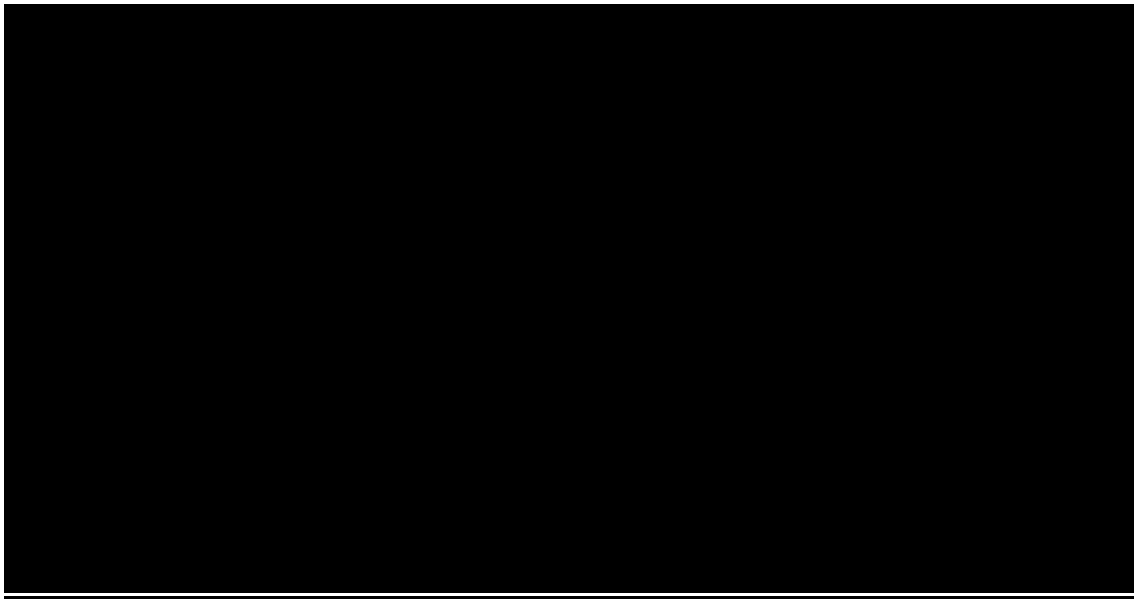
Figure 30: IPD meta-regression: time to first ≥ 10% decline in FVC % predicted over the whole trial duration for nerandomilast and nintedanib in IPF (top panel) and PPF (bottom panel)





Key: bid, twice a day; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib; NERA, nerandomilast; PPF, progressive pulmonary fibrosis.
Notes: IPF analyses based on 198 events among 510 patients in the placebo group, 157 events among 638 patients in the NDB 150 mg bid group, 24 events among 87 patients in the NERA 18 mg bid group and 20 events among 88 patients in the NERA 9 mg group. PPF analyses based on 217 events among 553 patients in the placebo group, 97 events among 332 patients in the NDB 150 mg bid group, 59 events among 220 patients in the NERA 18 mg bid group, and 53 events among 220 patients in the NERA 9 mg bid group.
Source: Technical report for IPD meta-regression.[102]

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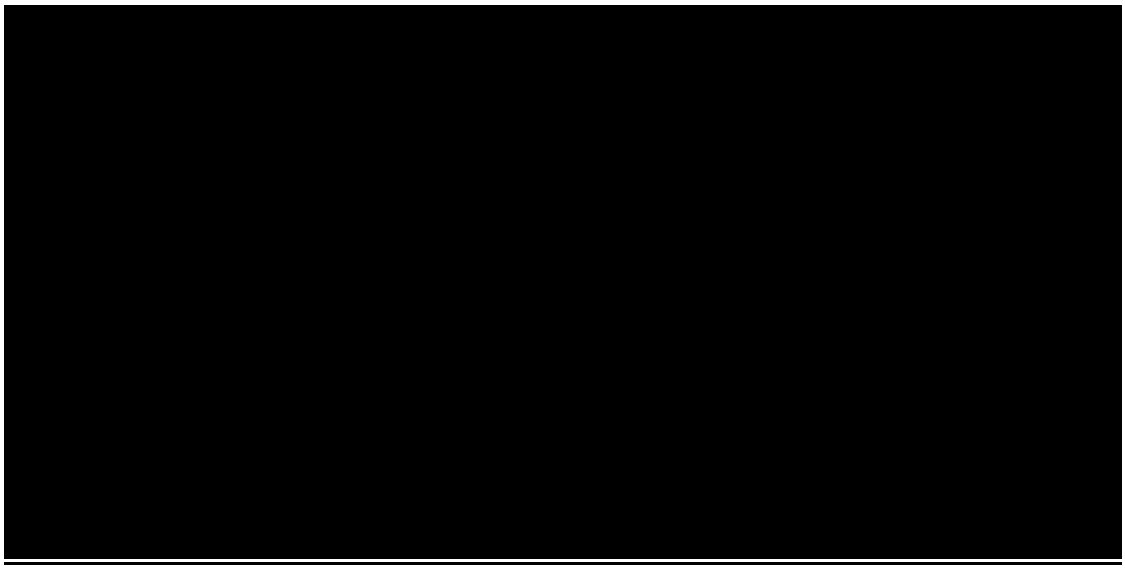
Figure 31: IPD meta-regression: change from baseline in FVC (mL) for nerandomilast and nintedanib in IPF (top panel) and PPF (bottom panel)





Key: bid, twice a day; FVC, forced vital capacity; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib; NERA, nerandomilast; PPF, progressive pulmonary fibrosis.
Notes: Dashed line indicates 52 weeks' timepoint.
Source: Technical report for IPD meta-regression.[102]

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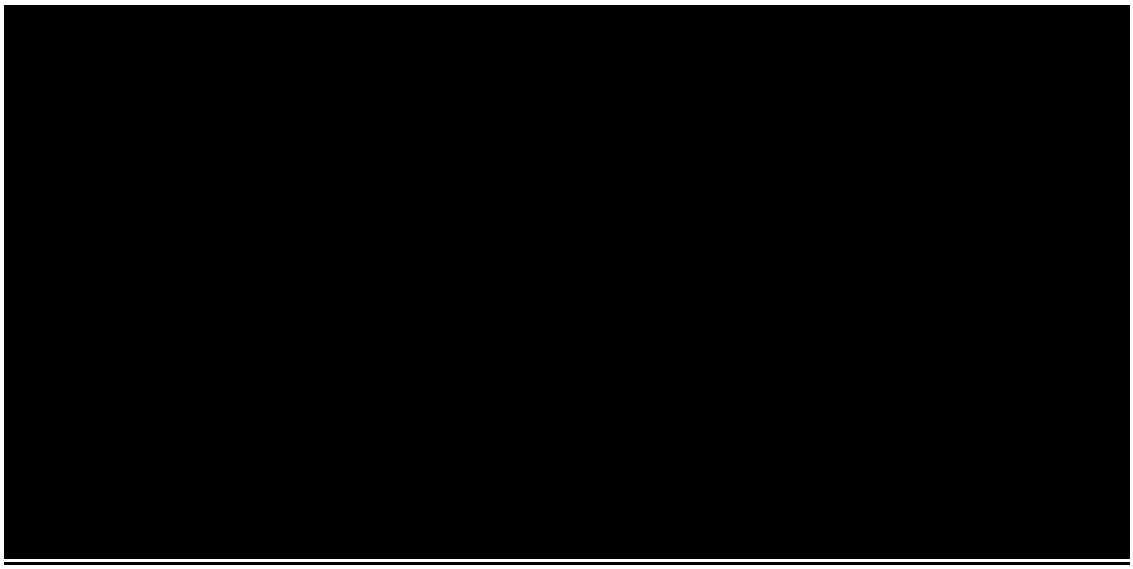
Figure 32: IPD meta-regression: change from baseline in FVC % predicted for nerandomilast and nintedanib in IPF (top panel) and PPF (bottom panel)





Key: bid, twice a day; FVC, forced vital capacity; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; NERA, nerandomilast; PPF, progressive pulmonary fibrosis.
Notes: Dashed line indicates 52 weeks' timepoint.
Source: Technical report for IPD meta-regression.[102]

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2.10.5 Uncertainties in the indirect and mixed treatment comparisons

Despite the availability of IPD for both nerandomilast and nintedanib that allowed for the most methodologically robust, population-adjusted comparisons possible, the IPD meta-regression method and outcomes are not without limitations as discussed below.

First, although the use of placebo as a common anchor reduces the risk of bias arising from differences in prognostic factors, the approach still rests on the assumption of conditional constancy of relative effects. This assumption requires that all important effect modifiers are correctly identified, measured and specified in the model. While expert feedback from clinicians was incorporated to identify relevant effect modifiers, the small number of events and the need to avoid overfitting necessitated retaining only variables with statistically significant associations in the final models. Consequently, the assumption may not be fully satisfied, and treatment effect estimates should be interpreted with caution. In addition to unmeasured or unreported covariates, other forms of missing information (e.g. missing outcomes or baseline characteristics) may also introduce bias.

Second, several endpoints (particularly death, respiratory related death and acute exacerbations) had very low event counts. These sparse data limited statistical power and reduced the precision and reliability of treatment effect estimates.

Finally, as with any population-adjustment method, adjustment can only be made for observed patient characteristics and, in some cases, for definitions of outcomes. Unobserved or unmeasured differences between studies may still remain, potentially leading to residual bias.

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2.11 Adverse reactions

2.11.1 Safety outcomes from individual FIBRONEER trials

2.11.1.1 Summary of treatment-emergent adverse events

Any side effects that started any time from the first dose of the trial medication to 7 days after the last dose were considered treatment-emergent adverse events (TEAEs).

2.11.1.1.1 FIBRONEER-IPF

An overall summary of TEAEs for treated patients up to DBL1 and DBL2 is presented in Table 20 for the monotherapy population of FIBRONEER-IPF. The equivalent summary for the Treated Set (TS) population is provided in Appendix K.

At both DBL1 and DBL2, a lower proportion of patients in the nerandomilast 18 mg bid group had one or more of: any AEs, severe AEs (Grade ≥ 3), AEs leading to treatment discontinuation, AEs leading to treatment interruption and serious AEs, compared with placebo (Table 20). Nerandomilast 18 mg bid was also linked to a lower rate of serious AEs resulting in death compared with placebo [redacted] at DBL2).[103]

A higher proportion of patients in the nerandomilast 18 mg bid group had one or more treatment-related adverse event (TRAE) at DBL1 and DBL2 compared with placebo (Table 20). This was primarily driven by higher rates of diarrhoea (see Section 2.11.1.2).[103]

The most commonly reported AEs at the System Organ Class (SOC) level for nerandomilast 18 mg bid and placebo groups of the monotherapy population were infections and infestations (DBL2:[redacted]), gastrointestinal disorders [redacted], and respiratory, thoracic and mediastinal disorders ([redacted]).[105] The most commonly reported AEs at the preferred term (PT) level were diarrhoea (discussed below in Section 2.11.1.2), COVID-19 [redacted] and upper respiratory tract infection [redacted]. Frequencies of AEs at SOC and PT levels were comparable at DBL1 and DBL2.[105]

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For full details of the most commonly reported AEs at the SOC and PT level, please refer to Appendix D.

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Table 20: Overall summary of AEs up to DBL1 and DBL2, FIBRONEER-IPF ('no AF background therapy' cohort)

	DBL1						DBL2					
	Nerandomilast 18 mg bid (N = 87)		Nerandomilast 9 mg bid (N = 88)		Placebo (N = 87)		Nerandomilast 18 mg bid (N = 87)		Nerandomilast 9 mg bid (N = 88)		Placebo (N = 87)	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Patients with any AE	79 (90.8)	[redacted]	79 (89.8)	[redacted]	85 (97.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe AEs (CTCAE Grade ≥ 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigator-defined drug-related AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to permanent treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to temporary treatment interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	23 (26.4)	[redacted]	27 (30.7)	[redacted]	31 (35.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resulted in death	0	0	3 (3.4)	[redacted]	8 (9.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; AF, antifibrotic; CTCAE, Common Terminology Criteria for Adverse Events; DBL1, Database lock 1; DBL2, Database lock 2; IPF, idiopathic pulmonary fibrosis; PY, person year.
Source: Richeldi et al. 2025[28]; FIBRONEER-IPF CTR [Table 12: 17 and Table 12: 18).[103]

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2.11.1.1.2 FIBRONEER-ILD

An overall summary of TEAEs for treated patients up to DBL1 and DBL2 is presented in Table 21 for the monotherapy population of FIBRONEER-ILD. The equivalent summary for the TS population is provided in Appendix L.

At both DBL1 and DBL2, compared with placebo, a lower proportion of patients in the nerandomilast 18 mg bid group had one or more of: any AEs, severe AEs (Grade ≥ 3), AEs leading to treatment discontinuation, AEs leading to treatment interruption or serious AEs (Table 21). Nerandomilast 18 mg bid was also linked to a lower rate of serious AEs resulting in death compared with placebo (DBL2: [redacted]).[104]

Compared with the placebo group, a higher proportion of patients in the nerandomilast 18 mg bid group, had one or more TRAEs at DBL1 and DBL2 (Table 21). As was the case in FIBRONEER-IPF this was primarily driven by higher rates of diarrhoea (see Section 2.11.1.2).[104]

The most commonly reported AEs at the SOC level for nerandomilast 18 mg bid and placebo groups of the monotherapy population were infections and infestations (DBL2:[redacted]), gastrointestinal disorders ([redacted]), and respiratory, thoracic and mediastinal disorders ([redacted]).[106] The most commonly reported AEs at the PT level were diarrhoea (discussed below in Section 2.11.1.2), cough ([redacted]) and upper respiratory tract infection ([redacted]). Frequencies of AEs at SOC and PT levels were comparable at DBL1 and DBL2.[106]

For full details of the most commonly reported AEs at the SOC and PT level, please refer to Appendix D. In the subsequent sections we present data for the most important adverse event of special interest (AESI) relating to nerandomilast.

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Table 21: Overall summary of AEs for DBL1 and DBL2 in FIBRONEER-ILD ('no AF background therapy' cohort)

	DBL1						DBL2					
	Nera 18 mg bid (N = 220)		Nerandomilast 9 mg bid (N = 220)		Placebo (N = 222)		Nera 18 mg bid (N = 220)		Nerandomilast 9 mg bid (N = 220)		Placebo (N = 222)	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Patients with any AE	203 (92.3)	[redacted]	206 (93.6)	[redacted]	207 (93.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe AEs (CTCAE Grade ≥ 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigator-defined drug-related AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to permanent treatment discontinuation	21 [redacted]	[redacted]	22 (10.0)	[redacted]	28 (12.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to temporary treatment interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	80 (36.4)	[redacted]	85 (38.6)	[redacted]	98 (44.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resulted in death	5 (2.3)	[redacted]	14 (6.4)	[redacted]	16 (7.2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; AF, antifibrotic; bid, twice a day; CTCAE, Common Terminology Criteria for Adverse Events; DBL1, Database lock 1; DBL2, Database lock 2; FAS, full analysis set; nera, nerandomilast; PY, person year.
Source: Maher et al. 2025[100]; FIBRONEER-ILD CTR (Table 12: 18)[104]; FIBRONEER-ILD CSAP (Table 69.3.1.1.1.1).[106]

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2.11.1.2 Diarrhoea

A detailed overview of diarrhoea events reported in the monotherapy population of the FIBRONEER trial programme is provided in Table 22.

The proportion of patients reporting diarrhoea was numerically higher in the nerandomilast 18 mg bid group compared with placebo at DBL1 (FIBRONEER-IPF: [redacted] FIBRONEER-ILD: [redacted]) and DBL2 (FIBRONEER-IPF: [redacted] FIBRONEER-ILD: [redacted]).

However, in both trials, diarrhoea leading to permanent discontinuation of nerandomilast 18 mg bid was infrequent (≤ 5% of those reporting at least one diarrhoea AE; Table 22). Most diarrhoea AEs reported were mild in intensity (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1, i.e. increase of < 4 stools/day), with [redacted] Grade 3 or higher diarrhoea AEs reported in FIBRONEER-IPF and [redacted] Grade 3 diarrhoea AEs in FIBRONEER-ILD up to DBL2 ([redacted] in the nerandomilast 9 mg bid group).[103, 104]

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Table 22: Summary of diarrhoea AEs up to DBL1 and DBL2, FIBRONEER-IPF ('no AF background therapy' cohort)

n (%[a])	DBL1			DBL2		
	Nera 18 mg bid	Nera 9 mg bid	Placebo	Nera 18 mg bid	Nera 9 mg bid	Placebo
FIBRONEER-IPF	N = 87	N = 88	N = 87	[redacted]	[redacted]	[redacted]
Patients with at least 1 AE 'diarrhoea'	23	15	7	[redacted]	[redacted]	[redacted]
Grade 1[b] (increase of < 4 stools/day)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2[b] (increase of 4–6 stools/day)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3[b] (increase of ≥ 7 stools/day)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigator-assessed TRAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Permanent discontinuation of trial drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious diarrhoea AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIBRONEER-ILD	N = 220	N = 220	N = 222	[redacted]	[redacted]	[redacted]
Patients with at least 1 AE 'diarrhoea'	59	35	35	[redacted]	[redacted]	[redacted]
Grade 1[b] (increase of < 4 stools/day)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2[b] (increase of 4–6 stools/day)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3[b] (increase of ≥ 7 stools/day)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigator-assessed TRAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Permanent discontinuation of trial drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious diarrhoea AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; AF, antifibrotic; bid, twice a day; CTCAE, Common Terminology Criteria for Adverse Events; DBL1, Database lock 1; DBL2, Database lock 2; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; nera, nerandomilast; TRAE, treatment-related adverse event.
Notes: [a] as percentage of patients with at least 1 AE 'diarrhoea'; [b] CTCAE grade.
Source: Richeldi et al. 2025[28]; Maher et al. 2025[100]; FIBRONEER-IPF CTR (Table 12: 30 and Table 12: 31)[103]; FIBRONEER-ILD CTR (Table 12: 32 and Table 12: 33).[104]

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2.11.1.3 Weight decrease

A detailed overview of weight decrease events reported in the monotherapy population of the FIBRONEER trial programme is provided in Table 23.

The proportion of patients reporting weight decrease was numerically higher in the nerandomilast 18 mg bid group compared with placebo at DBL1 (FIBRONEER-IPF: 8.0% versus 5.7%; FIBRONEER-ILD: 12.7% versus 5.0%) and DBL2 (FIBRONEER-IPF: [redacted]FIBRONEER-ILD: [redacted].[103, 104] However, no serious AEs, severe (CTCAE Grade 3) AEs or AEs leading to treatment discontinuation in the safety topic 'weight decrease' were reported in either trial.[103, 104]

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Table 23: Summary of weight decrease AEs up to DBL1 and DBL2, FIBRONEER-IPF and FIBRONEER-ILD ('no AF background therapy' cohorts)

	DBL1			DBL2		
	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo
FIBRONEER-IPF						
Patients with weight decrease (n/N, %)	7/87 (8.0)	2/88 (2.3)	5/87 (5.7)	[redacted]	[redacted]	[redacted]
HR vs placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIBRONEER-ILD						
Patients with weight decrease (n/N, %)	28/220 (12.7)	18/220 (8.2)	11/222 (5.0)	[redacted]	[redacted]	[redacted]
HR vs placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; AF, antifibrotic; bid, twice a day; CI, confidence interval; DBL1, Database lock 1; DBL2, Database lock 2; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis.
Source: Richeldi et al. 2025[28]; Maher et al. 2025[100]; FIBRONEER-IPF CTR (Table 15.3.1.1.5.6: 9)[103]; FIBRONEER-IPF CSAP (Table 47.3.1.1.4.3.1).[105]; FIBRONEER-ILD CTR (Table 15.3.1.1.5.6: 9)[104]; FIBRONEER-ILD CSAP (Table 69.3.1.1.3.3.1).[106]

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2.11.1.4 Drug-induced liver injury (DILI)

[redacted] in the monotherapy population of FIBRONEER-IPF were reported to have an AESI of 'potential severe DILI' up to DBL2.[103]

[redacted] in the monotherapy population of FIBRONEER-ILD were reported to have an AESI of 'potential severe DILI' up to DBL2.[104] [redacted] in the placebo group experienced hepatic failure, [redacted] in the placebo group experienced aspartate aminotransferase increase and [redacted] in the nerandomilast 9 mg bid group experienced DILI; [redacted] in the monotherapy population receiving nerandomilast 18 mg bid experienced a 'potential severe DILI'.[104]

2.11.1.5 Psychiatric events

The majority of patients in all treatment groups of both FIBRONEER trials did not show suicidal ideation or behaviour. Completed suicide was not observed during treatment in any of the treatment groups in either trial.[103, 104]

A slightly higher proportion of patients in the monotherapy population of FIBRONEER-IPF experienced an SOC event of psychiatric disorder in the nerandomilast 18 mg bid group compared with the placebo group of FIBRONEER-IPF at DBL2: [redacted] The most common psychiatric disorders experienced were depression, anxiety and insomnia, as summarised in Table 24. In FIBRONEER-ILD, a slightly lower proportion of patients in the monotherapy population experienced an SOC event of psychiatric disorder in the nerandomilast 18 mg bid group compared with placebo group of FIBRONEER-IPF at DBL2: [redacted]. The most common psychiatric disorders experienced were depression and anxiety, as summarised in Table 24.

Completed suicide was not observed during treatment in any of the treatment groups in either trial. Suicidal ideation was reported in [redacted] treated with nerandomilast monotherapy in FIBRONEER-IPF: [redacted] in the nerandomilast 18 mg bid group and [redacted] in the nerandomilast 9 mg bid group.[105] Suicidal ideation was reported in [redacted] treated with nerandomilast monotherapy in FIBRONEER-IPF: [redacted] in the nerandomilast 18 mg bid group and [redacted]

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[redacted]in the nerandomilast 9 mg bid group.[106] [redacted].[105, 106]

Table 24: Summary of common psychiatric AEs (≥ 5%) up to DBL2, FIBRONEER-IPF and FIBRONEER-ILD ('no AF background therapy' cohorts)

	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo
FIBRONEER-IPF	N = 87	N = 88	N = 87
Psychiatric disorder	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]
FIBRONEER-ILD	N = 220	N = 220	N = 222
Psychiatric disorder	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; AF, antifibrotic; bid, twice a day; CI, confidence interval; DBL2, Database lock 2; IPF, idiopathic pulmonary fibrosis.
Source: FIBRONEER-IPF CSAP (Table 47.3.1.1.1.2)[105]; FIBRONEER-ILD CSAP (Table 69.3.1.1.1.2).[106]

2.11.2 Safety outcomes from pooled analyses of FIBRONEER trials

Results for pooled analyses of FIBRONEER-IPF and FIBRONEER-ILD for the monotherapy population are presented in Table 25.

Nerandomilast 18 mg bid monotherapy, compared with placebo, was associated with a lower rate of severe AEs ([redacted]), AEs leading to permanent treatment discontinuation ([redacted]), serious AEs ([redacted]) and serious AEs resulting in death ([redacted]).[101] In contrast, nerandomilast 18 mg bid was linked to a higher rate of investigator-defined drug-related AEs compared with placebo ([redacted]).

Although nerandomilast 18 mg bid monotherapy was associated with a higher rate of diarrhoea AEs across pooled trials versus placebo (DBL2:[redacted]), there were no instances of serious or severe diarrhoea in either treatment arm.[101] Only [redacted] patients permanently discontinued nerandomilast due to diarrhoea.

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Weight decrease as an AE was slightly more frequent in the nerandomilast 18 mg bid arm compared with placebo ([redacted]), but there were [redacted] serious or severe AEs of weight decrease.[101] Only [redacted] discontinued nerandomilast due to weight decrease, compared with none in the placebo arm.

There were [redacted] of 'DILI' reported at the PT level in either the nerandomilast 18 mg bid or the placebo treatment arm (in the placebo arm, [redacted] of 'Aspartate aminotransferase increase' and [redacted] of 'Hepatic failure' were reported – see Section 2.11.1.4).[101]

Table 25: Overall summary of AEs up to DBL2, FIBRONEER-IPF and FIBRONEER-ILD pooled ('no AF background therapy' cohort)

	Nerandomilast 18 bid mg (N = 307)		Nerandomilast 9 mg bid (N = 308)		Placebo (N = 309)	
	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY	n (%)	Rate/ 100 PY
Patients with any AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe AEs (CTCAE Grade ≥ 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigator-defined drug-related AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to permanent treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to temporary treatment interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resulted in death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; AF, antifibrotic; CTCAE, Common Terminology Criteria for Adverse Events; DBL2, Database lock 2; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis; PY, person year.
Source: FIBRONEER-IPF and -ILD pooled analyses (Table 85.2.2.1.1.1).[101]

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2.11.3 Safety outcomes from indirect treatment comparison

IPD meta-regression outcomes demonstrated a favourable safety and tolerability profile for nerandomilast 18 mg bid monotherapy compared with nintedanib 150 mg bid.[102] An overview of key safety outcomes for nerandomilast 18 mg bid versus nintedanib 150 mg bid in IPF and PPF (population-adjusted model) is provided in Table 26.

In IPF and PPF, nerandomilast 18 mg bid showed significantly longer TTD (IPF HR: [redacted]; PPF HR: [redacted]; Figure 33) and a significantly lower proportion of patients experiencing gastrointestinal disorders (IPF odds ratio [OR]: [redacted]; PPF OR: [redacted]) versus nintedanib 150 mg bid.

In IPF, nerandomilast 18 mg bid also showed numerical reductions in the proportion of patients experiencing serious AEs (OR: [redacted]), treatment discontinuations due to AE (OR: [redacted]) and diarrhoea (OR: [redacted]), versus nintedanib 150 mg bid. In PPF, nerandomilast 18 mg bid also showed significant reductions versus nintedanib 150 mg bid in the proportion of patients experiencing treatment discontinuation due to AEs (OR: [redacted]) and diarrhoea (OR: [redacted]).

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Table 26: IPD meta-regression: overview of key safety outcomes for nerandomilast versus nintedanib in IPF and PPF

Nerandomilast 18 mg bid vs nintedanib 150 mg (over the whole trial)	IPF	PPF
Time to treatment discontinuation, HR (95% CI)	[redacted]*	[redacted]*
Proportion of patients experiencing serious AE, OR (95% CI)	[redacted]*	[redacted]
Proportion of patients with treatment discontinuation due to AE, OR (95% CI)	[redacted]*	[redacted]*
Proportion of patients experiencing diarrhoea, OR (95% CI)	[redacted]**	[redacted]*
Proportion of patients experiencing GI disorders, OR (95% CI)	[redacted]*	[redacted]*

Key: AE, adverse event; bid, twice a day; CI, confidence intervals; GI, gastrointestinal; HR, hazard ratio; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; OR, odds ratio; PPF, progressive pulmonary fibrosis.
Notes: * Indicates significant benefit in favour of nerandomilast; ** indicates numerical benefit in favour of nerandomilast.
Source: Technical report for IPD meta-regression.[102]

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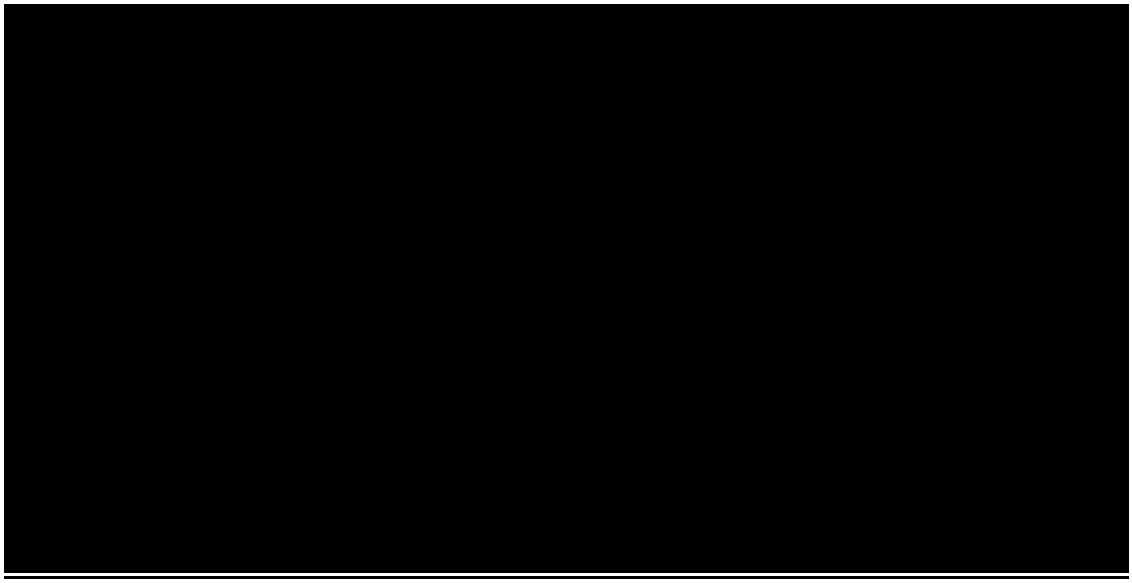
Figure 33: IPD meta-regression: time to treatment discontinuation over the whole trial duration for nerandomilast and nintedanib in IPF (top panel) and PPF (bottom panel)





Key: bid, twice a day; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib; NERA, nerandomilast; PPF, progressive pulmonary fibrosis**.**
Notes: IPF analyses based on 99 events among 510 patients in the placebo group, 151 events among 638 patients in the NDB 150 mg bid group, 11 events among 87 patients in the NERA 18 mg bid group and 19 events among 88 patients in the NERA 9 mg bid group. PPF analyses 165 events among 553 patients in the placebo group, 110 events among 332 patients in the NDB 150 mg bid group, 56 events among 220 patients in the NERA 18 mg bid group and 59 events among 220 patients in the NERA 9 mg bid group.
Source: Technical report for IPD meta-regression.[102]

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2.11.4 Safety overview

While nearly all patients in the monotherapy population of both FIBRONEER trials experienced an AE, nerandomilast 18 mg bid (no AF background therapy cohort) was associated with a lower rate of severe AEs, AEs leading to permanent treatment discontinuation, serious AEs, and serious AEs resulting in death compared with placebo.[103, 104]

Furthermore, nerandomilast 18 mg bid monotherapy offers a favourable safety profile compared with nintedanib, as evidenced by IPD meta-regression showing significantly longer TTD and a significantly lower proportion of patients experiencing gastrointestinal disorders for nerandomilast versus nintedanib in IPF and PPF.[102] In IPF, IPD meta-regression also showed numerical reductions in the proportion of patients experiencing serious AEs and treatment discontinuations due to AE; in PPF, significant reductions in the proportion of patients experiencing treatment discontinuation due to AEs were shown.[102]

The most common AE that occurred in the nerandomilast 18 mg bid group of both FIBRONEER trials was diarrhoea; however, it was considered medically manageable, with no serious or severe diarrhoea observed over the trials' durations.[103, 104] Importantly, the rate of diarrhoea was numerically lower (IPF) or significantly lower (PPF) for nerandomilast 18 mg bid monotherapy compared with nintedanib 150 mg bid (see Section 2.11.2).[102] Nerandomilast shows ~10 fold selectivity for the PDE4B isoenzyme over PDE4A, PDE4C and most importantly PDE4D, which has been most strongly linked with the gastrointestinal side effects of currently marketed PDE4 inhibitors in other therapy areas.[24]

In both FIBRONEER trials, no differences were reported between treatment groups in any other safety topic potentially related to nerandomilast's mode of action or risks of other PDE4 inhibitors, or any AESIs. Importantly, there were no reports of potential severe DILI in patients receiving nerandomilast 18 mg bid as a monotherapy in either trial up to DBL2. This low risk of liver toxicity associated with nerandomilast negates the requirement for repeat liver function monitoring that pose a burden to patients receiving current standard of care therapy (see Section 1.3.3.1.2).

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On consultation at a UK advisory board, clinical experts generally described the overall safety profile for nerandomilast as manageable and potentially favourable compared with current AF therapies.[81] Diarrhoea events were in line with expectations for a PDE4 inhibitor and not considered “excessive”. The dose-dependent tolerability and the ability to reduce the dose without losing efficacy was seen as a practical benefit in clinical settings, especially when managing side effects.[81]

2.12 Ongoing studies

Patients completing nerandomilast treatment in the FIBRONEER-ILD or FIBRONEER-IPF studies are eligible to enrol in the open-label extension trial, FIBRONEER-ON (NCT06238622). The primary goal of this study is to determine how well people tolerate long-term treatment with secondary goals around long-term effectiveness. Data from this extension trial will not be available until [redacted].

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Principal findings from the clinical evidence

Nerandomilast is the first preferential inhibitor of PDE4B with AF and immunomodulatory properties for people with IPF and PPF. Across the FIBRONEER trial programme, nerandomilast has demonstrated a robust, consistent and clinically meaningful efficacy profile.[87, 100]

Nerandomilast 18 mg bid monotherapy treatment of IPF (‘no AF background therapy’ cohort from the FIBRONEER-IPF trial) resulted in the following[105]:

- Slowing of disease progression, with a clinically meaningful relative reduction in lung function decline of 47% at 52 weeks, as measured by change in FVC versus placebo (−79.2 mL versus −148.7 mL)
- A clinically meaningful reduction in the risk of acute ILD exacerbation, hospitalisation for respiratory cause or death of [redacted] up to DBL2 versus placebo (HR: [redacted])

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- A clinically meaningful and nominally significant reduction in the risk of death of [redacted] up to DBL2 versus placebo (HR: [redacted])
- A clinically meaningful reduction in the risk of acute ILD exacerbation or death of [redacted] up to DBL2 versus placebo (HR: [redacted])
- A clinically meaningful extension in progression-free living with a reduction in the risk of FVC % predicted decline of >10% or death of [redacted] up to DBL2 versus placebo (HR: [redacted])
- A clinically meaningful reduction in the risk of needing supplemental oxygen of [redacted] up to DBL2 versus placebo (HR: [redacted])

Nerandomilast 18 mg bid monotherapy treatment of PPF ('no AF background therapy' cohort from the FIBRONEER-ILD trial) resulted in[106] the following:

- Slowing of disease progression, with a clinically meaningful relative reduction in lung function decline of 38% at 52 weeks, as measured by change in FVC versus placebo (−95.2 mL versus −154.1 mL)
- Early onset of effect and persistent improvement in pulmonary function in the first 12 weeks of use, as measured by an increase in FVC from baseline
- A clinically meaningful and nominally significant reduction in the risk of acute ILD exacerbation, hospitalisation for respiratory cause or death of [redacted] up to DBL2 versus placebo (HR: [redacted])
- A clinically meaningful and nominally significant reduction in the risk of death of [redacted] up to DBL2 versus placebo (HR: [redacted])
- A clinically meaningful and nominally significant reduction in the risk of acute ILD exacerbation or death of [redacted] up to DBL2 versus placebo (HR: [redacted])
- A clinically meaningful and nominally significant extension in progression-free living with a reduction in the risk of FVC % predicted decline of >10% or death of [redacted] up to DBL2 versus placebo (HR: [redacted])
- A clinically meaningful and nominally significant reduction in the risk of needing supplemental oxygen of [redacted] up to DBL2 versus placebo (HR: [redacted])

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In pooled analyses of the FIBRONEER trial programme, nerandomilast 18 mg bid monotherapy was shown to significantly[101]:

- Slow disease progression, with an adjusted mean difference in change from baseline to Week 52 in FVC of [redacted] (95% CI: [redacted]) versus placebo, representing a [redacted] relative reduction in lung function decline ([redacted])
- Reduce the risk of time to acute exacerbation, hospitalisation for respiratory cause or death versus placebo by [redacted] (HR: [redacted])
- Reduce the risk of acute exacerbation or death versus placebo by [redacted] (HR: [redacted])
- Reduce the risk of hospitalisation for respiratory cause or death versus placebo by [redacted] (HR: [redacted])
- Reduce the risk of death versus placebo by [redacted] (HR: [redacted])
- Extend the periods of progression-free living, reducing the risk of time to FVC % predicted decline of > 10% or death versus placebo by [redacted] (HR:[redacted])

Early and sustained improvements in pulmonary function within the first 12 weeks of treatment, as observed in FIBRONEER-ILD, has not been previously reported in pulmonary fibrosis and supports the novel mechanism of action of nerandomilast, including its dual targeting of fibrotic and inflammatory pathways.[81] Moreover, nerandomilast is the first treatment ever to demonstrate a survival benefit in an RCT setting for pulmonary fibrosis. Clinical experts note the mortality signal in the FIBRONEER clinical trial programme is particularly compelling with survival benefits only demonstrated in longer-term open-label follow-up studies of current AF therapies.[81]

In robust IPD meta-regression, nerandomilast 18 mg bid demonstrated a clinically meaningful efficacy profile, compared with current standard of care, in terms of:

- A clinically meaningful reduction in the risk of death of [redacted] in the IPF population and [redacted] in the PPF population versus nintedanib

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- Slowing disease progression, with a similar effect on reduction in lung function decline, as measured by the absolute change from baseline in FVC (mL and % predicted; slightly in favour of nerandomilast) and time to ≥10% FVC % predicted decline (slightly in favour of nintedanib)

This robust IPD meta-regression can be considered applicable to both nintedanib and pirfenidone in the IPF population, given the accepted clinical similarity of these treatments (see Section 2.10).

While the HRQL data captured in the FIBRONEER trial programme showed little difference across treatment arms, these findings may not fully reflect the real-world impact of nerandomilast. A new treatment that can slow disease progression and extend life without the tolerability concerns and monitoring burden of current AF therapies (see below) has the potential to deliver meaningful improvements in quality of life for patients and their loved ones in routine clinical practice. Clinical experts were not surprised or concerned that an HRQL benefit was not observed in the trial programme but believe that nerandomilast would be well-received by patients because of its mortality benefit plus fewer exacerbations – these factors are of greatest importance to patients.[81]

Of further importance to patients and healthcare professionals alike, nerandomilast 18 mg bid was also well tolerated. In both FIBRONEER trials, there were fewer AEs, serious AEs and fatal AEs reported in people treated with nerandomilast 18 mg bid compared with placebo (see Section 2.11). Current standard of care can be associated with liver damage and routine liver function monitoring via blood tests is recommended (nintedanib) or mandated (pirfenidone) with their use.[88-90] Patients can also suffer debilitating diarrhoea resulting in high volumes of dose reductions and treatment discontinuation (see Section 1.3.3.1.2) that reduces the potential for sustained disease control with current AF therapy.

Although diarrhoea was the most common AE observed in the FIBRONEER trial programme, events were generally mild in nature and medically manageable with very few discontinuations due to diarrhoea (Table 22). IPD meta-regression showed that nerandomilast 18 mg bid had significantly longer TTD and significantly lower proportion of patients experiencing gastrointestinal disorders in both IPF and PPF,

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supporting better tolerability of nerandomilast compared with the current standard of care (see Section 2.11.3). In real-world practice, clinicians will have the option of reducing the dose of nerandomilast to 9 mg bid to help them manage any side effects of nerandomilast, without compromising treatment effect, as demonstrated by clinical benefits of the nerandomilast 9 mg bid arm of the FIBRONEER trial programme. The tolerability profile, ability to reduce dose if needed without loss of effect and the absence of routine monitoring and dose titration requirements are all seen as important advantages of nerandomilast by the clinical community.[81]

2.13.2 Strengths and limitations of trial

The FIBRONEER trial programme provides high-quality RCT data investigating the clinical efficacy and safety of nerandomilast for people with IPF and PPF. Clinical experts have verified that placebo arm outcomes in the FIBRONEER trial programme reflect expected outcomes of the pulmonary fibrosis population receiving BSC in clinical practice.[81] It is therefore expected that the clinical benefit demonstrated in this trial programme will translate to the real-world population. Although the FIBRONEER trials do not provide head-to-head data versus current AF therapy, access to the IPD for nerandomilast and nintedanib pivotal trials is a unique advantage of this appraisal and allows robust ITC to address this evidence gap.

It should be acknowledged that the key secondary endpoint was not met in the FIBRONEER-IPF or FIBRONEER-ILD trials. The key secondary endpoint was a composite endpoint encompassing objective (death) and subjective components, with no independent adjudication of acute exacerbations or hospitalisations due to respiratory cause events. This composite approach was taken to try to provide an endpoint that is clinically meaningful and would capture a high enough number of events to include in statistical testing. On consultation, clinical experts in the UK approached interpretation of this endpoint with a mix of clinical pragmatism and statistical caution but were unanimous in their encouragement of the positive and promising trends shown in individual components of the composite endpoint.[81]

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Multiple UK sites were included in the FIBRONEER trial programme, and a total of 48 UK patients were enrolled – 18 to FIBRONEER-IPF and 30 to FIBRONEER-ILD. At a UK advisory board involving 12 ILD-treating clinical experts in the UK, the general consensus was that trial populations are representative of people with progressive fibrotic ILD in clinical practice.[81] While some differences were observed in the demographic profile (age and sex) and clinical characteristics (comorbidities, underlying ILD diagnoses, histological pattern), this is reflective of the highly heterogeneous patient population under investigation. Indeed, the diversity in the clinical trial population is a key strength of the FIBRONEER trial programme, supported by the clinical community.[81]

The biggest applicability concern raised by the experts was in relation to concomitant immunosuppressant medication rules applied in the FIBRONEER-ILD trial.[81] Mycophenolate and rituximab are two of the most common immunosuppressants used to manage PPF in UK clinical practice but people receiving such treatment were not eligible for enrolment to FIBRONEER-ILD. While there is no biological reason why the type of immunosuppressant therapy should impact the expected outcomes of treatment with nerandomilast, it may have impacted the severity of disease profile of patients. However, this was not observed in the disease characteristics.

Differences in background AF therapy use were also discussed but concluded in an acknowledgement of regional treatment patterns in the UK.[81] Some centres reported up to 40% use of AF therapy in the PPF population and up to 80% use of AF therapy in the IPF population, whereas others reported far lower prescription rates. In part at least, this is related to the ‘postcode lottery’ of access to ILD centres with some patients preferring to receive immunosuppressant treatment, if appropriate, and stay local rather than travel for specialist care. The focus of this submission and reimbursement application to use nerandomilast 18 mg bid as monotherapy negates any applicability concerns of background AF therapy use. Data for monotherapy are taken from the ‘no AF background therapy’ cohort of the FIBRONEER trials. While this was not the population for which the trials were statistically powered to test, it was a pre-specified subgroup in both trials, and randomisation was stratified by the presence of AF background therapy (yes versus no). The overall number of patients

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in the monotherapy subgroup of each trial may be a limitation of these analyses, however this was the result of constraints such as the requirement for ethical trial design and the challenge to recruit IPF patients with such poor prognosis who do not immediately receive available licensed therapies.

The current evidence base provides data up to 100 weeks, and therefore some extrapolation of data are required to model longer-term outcomes (see Section 3.3). A robust structured expert elicitation is being conducted to address this gap and longer-term data are being collected in the ongoing FIBRONEER-ON study.

In conclusion, nerandomilast 18 mg bid can address the clear and urgent unmet need for an effective, safe and well tolerated new treatment option for people living with IPF and PPF that can enable longer time on treatment to slow disease progression, extend life and preserve overall HRQL of patients. It is also shown to offer good value to the NHS in economic analyses presented in Section 3.

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3 Cost-effectiveness

Objective:

- To examine the cost-effectiveness of nerandomilast versus current treatment options for patients with IPF or PPF

Model overview:

- A de novo cohort-level Markov model was developed, with health states based on FVC % predicted in 10 percentage point intervals
- Analyses were conducted over a lifetime horizon from the English National Health Service (NHS) and Personal Social Services (PSS) perspective
- In IPF, the comparators were BSC, nintedanib and pirfenidone
- In PPF, the comparators were BSC and nintedanib

Key model inputs and assumptions:

- Clinical data (FVC changes, OS, risk of acute exacerbation and TTD) used in this economic analysis were based on the results from the pivotal FIBRONEER trials for nerandomilast and BSC, and INBUILD and INPULSIS trials for nintedanib
  - Health state transitions (change in FVC % predicted) were determined using a Poisson regression model
  - Extrapolations of OS, acute exacerbations and TTD were conducted in accordance with NICE technical support document (TSD) 14[119] to obtain long-term estimates to support the model
  - The base case OS extrapolations follow a gamma distribution, based on statistical and visual fit, and clinical plausibility of extrapolations[93, 116]
  - The base case applies a constant risk of acute exacerbation and treatment discontinuation per cycle, differentiated by treatment
  - The base case applies treatment waning to all efficacy outputs and assumes a stopping rule for all active treatments if the patient experiences a drop of FVC % predicted greater than 10%
- Health state utility values were informed by pooled EQ-5D-5L data collected in the FIBRONEER-IPF and INPULSIS trials (IPF) and FIBRONEER-ILD and INBUILD

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trials (PPF), mapped to the third-line (3L) value set using the mapping function developed by the NICE Decision Support Unit[120]

- Costs and HCRU captured in the analysis included drug acquisition and administration costs, liver function monitoring costs, monitoring costs, AE costs, acute exacerbation costs and end of life costs
  - Resource use frequencies were obtained from the FIBRONEER trials
  - The model included Grade 3+ AEs

Results:

- In the base case analysis in IPF, nerandomilast was associated with an ICER of [redacted] per QALY gained versus BSC, [redacted] per QALY gained versus nintedanib and [redacted] per QALY gained versus pirfenidone
- In the base case analysis in PPF, nerandomilast was associated with an ICER of [redacted] per QALY gained versus BSC and [redacted] per QALY gained versus nintedanib
- Results for both populations were most sensitive to mortality parameters, the length of the treatment waning effect, and treatment discontinuation probability
- The weighted average ICER for nerandomilast (assuming 87% of pulmonary fibrosis cases are IPF and 13% are PPF (Section 1.3.1.2)) was [redacted] per QALY gained versus BSC, and [redacted] per QALY gained versus nintedanib

3.1 Published cost-effectiveness studies

An SLR was conducted in September 2025 to identify relevant economic publications for both indications (IPF and PPF) using PRISMA guidelines[121]; full search methods and results are detailed in Appendix E.

3.2 Economic analysis

The de novo model described in the following sections was developed to assess the cost-effectiveness of nerandomilast monotherapy for treating adult patients with IPF or PPF from the perspective of the UK NHS and PSS. A de novo model was required as no existing economic evaluations of nerandomilast were identified. Key aspects

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from previous models that were used to inform the current submission are provided in the relevant sub-sections.

3.2.1 Patient population

The patient population evaluated is adults with IPF or PPF in line with the expected marketing authorisation for nerandomilast, with the modelled population based on FIBRONEER-IPF and FIBRONEER-ILD trial populations (no AF background therapy cohorts), respectively (Table 1). Baseline characteristics are summarised in Table 27 and baseline FVC distributions are reported in Section 3.3.2 (Table 29 for IPF and Table 31 for PPF). The FIBRONEER-IPF/-ILD populations have been validated by ILD specialists and treating clinicians as representative of UK clinical practice (see Section 2.13.2).[81]

Table 27: Summary of population inputs used in the model

Variable	FIBRONEER-IPF (IPF)	FIBRONEER-ILD (PPF)
Age (mean years, SE)	70.4, 0.5	66.2, 0.4
Male (%, N)	76.0, 262	49.8, 662
Key: IPF, idiopathic pulmonary fibrosis; N, number; PPF, progressive pulmonary fibrosis; SE, standard error.		

3.2.2 Model structure

The economic model was built in Microsoft Excel. Visual Basic for Applications was used for functions not feasible with standard Excel (such as running the deterministic model, the sensitivity and scenario analyses) and to enhance user-friendliness and model design, such as navigation and hide/show functionality.

The core model structure is a cohort-level Markov state transition approach, with health states based on FVC % predicted, with 3-month time cycles. In alignment with NICE guidelines, a lifetime time horizon was adopted to capture all relevant costs and health outcomes, all costs and outcomes were discounted at an annual rate of 3.5%, and a half-cycle adjustment was applied.[122] The adopted modelling approach is consistent with both previously published economic models and previous NICE technology appraisals for IPF and PPF, for which the main features are summarised

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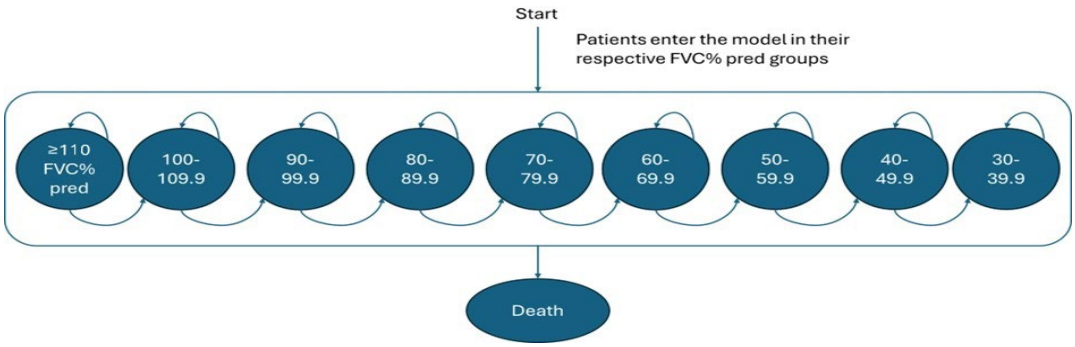
in Table 28. This model structure is also aligned with the key outcomes from the FIBRONEER trials, with FVC % predicted decline directly related to the primary endpoint (absolute change from baseline in FVC [mL] at Week 52) and to one of secondary endpoints (time to absolute decline in FVC % predicted of >10% from baseline or death over the trial duration; see Section 2.3).

The model includes a switch for selecting either an IPF or PPF population; doing so will change the selected inputs, while preserving a consistent model structure. The model consists of 10 mutually exclusive health states, as illustrated in Figure 34.

Health states are based on FVC % predicted in 10 percentage point intervals to capture disease progression in the base case, with different HCRU and utility associated with each health state. The FVC % predicted 10 percentage point width is consistent with the progressive nature of IPF/PPF and prior economic models in IPF/PPF[80, 123, 124] whilst also ensuring that transitions between health states reflect clinically important differences in FVC % predicted.[125-127] The lowest health state modelled is an FVC % predicted of 30–39.9, aligned with the clinical experts' opinion that life below an FVC % predicted of 30 becomes unsustainable.[116] This approach is consistent with prior NICE technology appraisals in IPF and PPF (see Table 28). In the base case, acute exacerbations can affect HCRU and patient utility. In a scenario, each FVC % predicted health state is duplicated to account for patients with a history of acute exacerbation having a different trajectory of FVC % predicted change than patients without a history of acute exacerbation.

Figure 34: Model structure



Key: FVC % pred, percent predicted forced vital capacity. **Notes:** In a scenario analysis, all the health states are duplicated and considered separately for those with and without a history of acute exacerbations.

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At the model start, the cohort is distributed across the FVC % predicted baseline as per the distributions observed in the FIBRONEER trials (see Section 3.3.2). During each 3-month model cycle, the cohort can:

1) Remain in the same FVC % predicted health state
2) Experience a loss of lung function (move to the next FVC % predicted health state)
3) Die

It is assumed that patients who progress to a lower FVC % predicted health state cannot move back to any health state with higher FVC % predicted. This is a conservative assumption for nerandomilast as FVC % predicted in the FIBRONEER trials was seen to initially improve for patients randomised to nerandomilast, but not for patients randomised to placebo, especially in PPF (Section 2.6.3). No such improvement was observed in any of the nintedanib or pirfenidone trials, therefore prior models and NICE appraisals in IPF and PPF did not model a short-term improvement.

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Table 28: Features of the current economic analysis, in comparison with prior NICE appraisals in IPF and PPF

Factor	TA504[51] (update of TA282)	TA379[18]	TA864[80]	TA747[47]	Current evaluation, chosen values	Current evaluation, justification
Indication	IPF	IPF	IPF	PPF (previously referred to as PF-ILD)	IPF and PPF	Consistent with NICE scope
Population	Scoped as mild to moderate IPF. FVC % predicted 50–80 was already recommended. Appraisal considered extension to include FVC % predicted 80–90 (with stopping rule)	Scope: IPF patients (no FVC % predicted – specifications) Recommended: FVC % predicted 50–80	FVC % predicted > 80	PF-ILD that has progressed despite treatment	People with IPF or PPF	Consistent with marketing authorisation
Intervention	Pirfenidone	Nintedanib	Nintedanib	Nintedanib	Nerandomilast monotherapy (18 mg bid)	Intervention of interest
Comparators	Nintedanib BSC	Pirfenidone BSC	Established clinical management	Established clinical management (immunosuppressants, corticosteroids, infliximab, rituximab, BSC)	IPF: NDB, PFN (FVC % predicted 50–80 only), BSC PPF:	Reflects the comparators used in clinical practice at the expected positioning of

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Factor	TA504[51] (update of TA282)	TA379[18]	TA864[80]	TA747[47]	Current evaluation, chosen values	Current evaluation, justification
					NDB, BSC	nerandomilast (see Table 1 and Section 1.3.4.3 for details)
Outcomes	Pulmonary function parameter, physical function, exacerbation rate, progression-free survival, mortality, adverse effects of treatment, health-related quality of life	Pulmonary function parameter, physical function, exacerbation rate, progression-free survival, mortality, adverse effects of treatment, health-related quality of life	Pulmonary function parameter, physical function, exacerbation rate, mortality, adverse effects of treatment, health-related quality of life	Pulmonary function parameter, physical function, exacerbation rate, lung transplantation, mortality, adverse effects of treatment, health-related quality of life	Pulmonary function, physical function, exacerbation rate, hospitalisation rate, mortality, adverse effects of treatment, health-related quality of life	Captures key outcomes
Perspective	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	NHS and PSS	Consistent with NICE reference case
Discounting	3.5% for costs and health benefits	3.5% for costs and health benefits	3.5% for costs and health benefits	3.5% for costs and health benefits	3.5% for costs and health benefits	Consistent with NICE reference case
Cycle length	3 months	3 months	3 months	3 months	3 months	Sufficient to capture changes in

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Factor	TA504[51] (update of TA282)	TA379[18]	TA864[80]	TA747[47]	Current evaluation, chosen values	Current evaluation, justification
						costs and health outcomes
Model health states	Health states: PF, PD and dead. Patients could not regress from PD to PF	Exacerbation and no-exacerbation both divided into FVC % predicted point categories (110 to 30 in decrements of 10) and dead	Exacerbation and no-exacerbation both divided into FVC % predicted point categories (110 to 30 in decrements of 10) and dead	Exacerbation and no-exacerbation both divided into FVC % predicted point categories (110 to 30 in decrements of 10) and dead	9 health states according to FVC % predicted point categories (110 to 30 in decrements of 10) and dead	Reflects clinically important changes in disease function, consistent with prior appraisals
Time horizon	34 years (lifetime)	Lifetime	Lifetime (50 years)	Lifetime	Lifetime	Consistent with NICE reference case
FVC progression	Disease progression defined as patients who experienced any of the following: • Confirmed ≥ 10% absolute decline in FVC % predicted	Baseline disease progression was defined as a 10-point drop in FVC % predicted every 3 months (constant risk)	Baseline disease progression was defined as a 10-point drop in FVC % predicted every 3 months (constant risk)	Baseline disease progression was defined as a 10-point drop in FVC % predicted every 3 months (constant risk)	Baseline disease progression was defined as a 10-point drop in FVC % predicted from baseline as well as a subsequent drop of 10% relative to baseline (all evaluated every	More accurate modelling of the change in FVC % predicted observed in FIBRONEER trials

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Factor	TA504[51] (update of TA282)	TA379[18]	TA864[80]	TA747[47]	Current evaluation, chosen values	Current evaluation, justification
	• Confirmed ≥ 50 m decline in 6MWD • Death				3 months, constant risk)	
Mortality	Fitted parametric curves for mortality using extrapolated mortality data	Modelled independently of other outcomes (exacerbations/progression). Odds ratio was applied to the BSC risk for the mortality risk of both arms. In the sensitivity analysis, it was assumed death could occur from a level of FVC % predicted of 30–39.9	Modelled independently of other outcomes (exacerbations/progression). Odds ratio was applied to the BSC risk for the mortality risk of both arms. In the sensitivity analysis, it was assumed death could occur from a level of FVC % predicted of 30–39.9	Modelled independently of other outcomes (exacerbations/progression). Odds ratio was applied to the BSC risk for the mortality risk of both arms. In the sensitivity analysis, it was assumed death could occur from a level of FVC % predicted of 30–39.9	Modelled independently of other outcomes (exacerbations/progression). Mortality risk modelled with pooled FIBRONEER and INPULSIS (IPF) or INBUILD (PPF) data	Consistent with previous approaches
Exacerbation	Acute exacerbation risk applied per cycle based on current treatment regardless of	Exacerbation assumed to be constant hazard within cycle length based on INPULSIS trial data. Differing per treatment arm and for investigator-reported vs	Exacerbation assumed to be constant hazard based on INPULSIS trial data. Differing per treatment arm and for investigator-reported vs adjudication Committee	Exacerbation assumed to be constant hazard based on INBUILD trial data. Differing per treatment arm	Exacerbation assumed to be constant hazard based on trial data. Differing per treatment arm	Consistent with previous approaches

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Factor	TA504[51] (update of TA282)	TA379[18]	TA864[80]	TA747[47]	Current evaluation, chosen values	Current evaluation, justification
	prior experience	adjudication Committee				
Hospitalisation	Included in the cost and utilities associated with acute exacerbations, based on the probability of hospitalisation in the pooled trial data (assumed to be the same for pirfenidone and nintedanib, but different for BSC)	Hospital costs based on 10% FVC % predicted-group-based probability of hospitalisation. Hospitalisations from INPULSIS data were used, which were based on hospitalisations due to respiratory causes and exacerbations	Hospital costs based on 10% FVC % predicted-group-based probability of hospitalisation. Hospitalisations from INPULSIS data were used, which were based on hospitalisations due to respiratory causes and exacerbations	Hospital costs based on 10% FVC % predicted-group-based probability of hospitalisation. Hospitalisations from INPULSIS data were used, which were based on hospitalisations due to respiratory causes and exacerbations	Hospital costs based on 10% FVC % predicted-group-based probability of hospitalisation. Hospitalisations from FIBRONEER data were used	Consistent with previous approaches
Stopping rule	Formal stopping rule included in model (company, EAG and Committee agreed that this improves the cost-	Formal stopping rule included in the model (primarily affecting costs). Neither nintedanib nor pirfenidone is cost-effective compared with BSC without a stopping rule.	Formal stopping rule was included in the model but removed as clinical experts deemed it difficult to implement (they would stop treatment if disease progression was not sufficiently slowed even without a	A formal stopping rule was not implemented because clinicians would stop treatment with nintedanib if they deemed that it was not effective	A formal stopping rule was applied in the base case to all active treatments.	There is a formal FVC based stopping rule for AFs in patients with FVC 50-80% predicted, and clinicians agreed that for

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Factor	TA504[51] (update of TA282)	TA379[18]	TA864[80]	TA747[47]	Current evaluation, chosen values	Current evaluation, justification
	effectiveness of treatments due to reduction in costs). Treatment is recommended only if treatment is stopped if there is evidence of disease progression (an absolute decline of 10% or more in FVC % predicted within any 12 months)	Treatment is recommended only if treatment is stopped if disease progresses (a confirmed decline in FVC % predicted of 10% or more) in any 12-month period	formal stopping rule and FVC % predicted is not the only measure for stopping treatment). The Committee acknowledged expert opinion and concluded that if nintedanib was cost-effective without a formal stopping rule, then no stopping rule would be applied. Recommended without stopping rule			PPF and IPF FVC > 80% they would also stop treatment if there is a significant decline in lung function[93]
Source of utilities	Mapping study due to unavailability	EQ-5D-3L from INPULSIS 1 and 2 trials	EQ-5D-3L from INPULSIS 1 and 2 trials	EQ-5D from the INBUILD trial	EQ-5D-5L from the FIBRONEER trials, mapped to 3L value set	Aligned with NICE preference to use trial-based EQ-5D when available
Source of costs	MIMS and NHS Reference	NHS Reference Costs, PSSRU,	NHS Reference Costs, PSSRU, NICE	NHS Reference Costs, PSSRU, NICE CG, Rincoig et al. (2007)	NHS Reference Costs, PSSRU, NICE CG,	NICE reference case[128]

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Factor	TA504[51] (update of TA282)	TA379[18]	TA864[80]	TA747[47]	Current evaluation, chosen values	Current evaluation, justification
	Costs and PSSRU	NICE CG full guideline (p163)	CG full guideline (p163)		Rincoig et al. (2007)	

Key: 3L, third-line; 6MWD, 6-minute walk distance; bid, twice a day; BSC, best supportive care; CG, clinical guideline; EAG, Evidence Assessment Group; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MIMS, Monthly Index of Medical Specialities; NDB, nintedanib; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PD, progressed disease; PF, progression-free; PF-ILD, progressive fibrosing interstitial lung disease; PFN, pirfenidone; PPF, progressive pulmonary fibrosis; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.
Note: PF-ILD refers to PPF.

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3.2.3 Intervention technology and comparators

As previously discussed, the intervention is nerandomilast, the first preferential inhibitor of PDE4B with both AF and immunomodulatory properties (see Table 2 in Section 1.2). Nerandomilast 18 mg bid is proposed to be used as monotherapy in people with IPF and PPF (see Section 1.3.4.3). Comparators for IPF are nintedanib, pirfenidone (recommended for people with FVC % predicted 50–80 only but included in the model irrespective of FVC % predicted based on discussions with clinicians[93]) and BSC. Comparators for PPF are nintedanib and BSC. Patients who are not suitable for, do not tolerate or have a lack or loss of response to AFs receive BSC.

3.3 Clinical parameters and variables

3.3.1 Source of evidence

The FIBRONEER trials (see Section 2.6) were the main clinical data source for the economic model, providing data on baseline characteristics, OS, time to first acute exacerbation, loss of lung function, TTD, and AEs. The data were based on the DBL2 (full trial duration) 'no AF background therapy' cohorts, which provides a direct comparison between nerandomilast 18 mg bid monotherapy versus BSC (placebo).[103, 104]

As the FIBRONEER trials did not include an active comparator, and nintedanib and pirfenidone were only used as background therapies in the 'AF background' cohort, any comparisons with those drugs were informed by ITCs, as outlined in Section 2.10. Inputs for non-trial comparators, including AE incidence, were primarily sourced from the INBUILD and INPULSIS studies (nintedanib)[123, 129] and the CAPACITY and ASCEND studies (pirfenidone).[130, 131] Unless stated otherwise, in the base case, the treatment effect was estimated using ITC results, with the relative efficacy of nerandomilast versus nintedanib assessed via IPD meta-regression. An alternative approach for nintedanib was explored in a scenario, using the INPULSIS (IPF) and INBUILD (PPF) trials pooled with the relevant FIBRONEER trial and incorporating treatment as a covariate to estimate the appropriate contrasts. Following clinical validation, and consistent with previously independently published ITCs[117, 118] and committee decision in TA379[18] "*that the clinical effectiveness of nintedanib is similar to pirfenidone"* (see Section 2.10.3.2), the treatment effect

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established for nintedanib via IPD meta-regression was assumed to apply to pirfenidone.[93, 116]

3.3.2 Change in FVC over time

Data for health state transitions were derived from analyses of patient-level data from the FIBRONEER trials, based on Poisson regression models with treatment regimen as a predictor.[103, 104] The Poisson regression model estimated a constant rate of FVC % predicted decline of 10%, counting as an event each loss of 10% from baseline (i.e. first drop being 10% and every subsequent drop being 10% relative to baseline).

In previous appraisals, disease progression was modelled using a logistic regression approach, with an event defined as either a ≥ 10% decrease in FVC % predicted compared with the previous value or crossing a health state threshold (those used to define the model health states), both within a given 3-month period. When applied to data from the FIBRONEER trials, this method produced implausible results. This is because logistic regression does not model longitudinal changes in FVC % predicted, such as the improvements observed in the nerandomilast arms of the FIBRONEER trials. When patients experienced an initial increase in FVC % predicted, subsequent declines from that improved value were counted as progression events, even when the patient's FVC % predicted remained above their baseline value. This led to a counterintuitive outcome in which nerandomilast appeared to have a higher risk of progression than placebo, despite trial evidence showing a benefit (see Section 2.6.3). Furthermore, because logistic regression measures change relative to the prior observation rather than baseline, it is highly sensitive to random short-term fluctuations in FVC measurements, amplifying noise and distorting long-term progression estimates.

Based on these limitations and an assessment of the results of the FIBRONEER trials, Poisson regression was selected for the current analysis, because it better reflects the disease trajectory observed in the FIBRONEER trials and addresses the aforementioned limitations associated with logistic regression. In the Poisson approach, progression events are measured relative to baseline FVC % predicted, rather than the most recent value. Each drop by 10% FVC % predicted relative to

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baseline counts as an event. This significantly reduces the impact of random variation and prevents penalising treatments that produce early improvements. While Poisson regression does not explicitly capture improvements, it ensures that any later decline is only considered progression if the patient's FVC falls below baseline, thereby mitigating the limitations with logistic regression. As a result, the estimates generated are more consistent with the observed trial data and better align with the known clinical effect of nerandomilast.

In addition to accurately capturing declines in FVC for nerandomilast, advantages of the Poisson regression approach are:

- All trial events are captured, unlike the logistic regression approach, which only captured events occurring within a 3-month period
- It increases statistical power by capturing continuous small declines in FVC % predicted
- Results are aligned with those observed in the trial; nerandomilast has a favourable effect on FVC % predicted decline compared with BSC

Poisson regression has previously been used in NICE technology appraisals where short-term data may lead to bias when using logistic regression. For example, in TA984[124], cardiovascular related hospitalisation rates were modelled using a Poisson framework to account for event rates over time without introducing bias from short-term measurement variability. NICE Decision Support Unit TSD 2 also highlights this as an appropriate approach to analyse event data.[132] This precedent supports the methodological robustness of using Poisson regression for the FIBRONEER trials' analyses and demonstrates its acceptance in other therapeutic areas where similar statistical challenges exist.

To reflect differences in progression risk by baseline lung function, the model was stratified by the median baseline FVC % predicted levels recorded in FIBRONEER-IPF and FIBRONEER-ILD (FVC % predicted 80 in IPF and 70 in ILD). Additionally, a scenario analysis was undertaken in which progression events following acute exacerbations were censored and an acceleration factor was applied, consistent with prior economic models, to reflect the increased progression risk post-exacerbation. The acceleration factor was sourced from external evidence to ensure

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methodological consistency, as acute exacerbations were defined and recorded differently across trials. For example, INPULSIS included investigator-reported and adjudicated events, while FIBRONEER used confirmed and suspected events without adjudication, reflecting differences in trial design and prevailing clinical definitions at the time. These variations in data capture were the reason the FIBRONEER exacerbation data were not used in the base-case analysis.

While Poisson regression addresses the key problems associated with logistic regression, there are limitations with this approach as the Poisson regression approach does not capture the early health benefits resulting from FVC improvement. This means the model assumes no early increase in FVC in any treatment arm, conservatively omitting an efficacy benefit of nerandomilast. This limitation could not be addressed through sensitivity analysis, as it was not possible to robustly model early FVC changes within the available data constraints. Additional details on the approach to modelling change in FVC over time are provided in Appendix M.

3.3.2.1 IPF

The baseline FVC distribution in the 'no background AF therapy' cohorts of the FIBRONEER-IPF trial is presented in Table 29.[103]

Table 29: Baseline FVC distribution for IPF used in the model

FVC % predicted	FIBRONEER-IPF (N = 262)
≥ 110	[redacted]
100–109.9	[redacted]
90–99.9	[redacted]
80–89.9	[redacted]
70–79.9	[redacted]
60–69.9	[redacted]
50–59.9	[redacted]
40–49.9	[redacted]
30–39.9	[redacted]
Key: FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.	

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In the base case, FVC % predicted decline is modelled using constant transition rates from FIBRONEER-IPF data, with health state transitions for nintedanib and pirfenidone assumed equal to nerandomilast. This assumption was made because IPD meta-regression showed no clinically meaningful differences in FVC decline between nerandomilast and nintedanib, with slight numerical benefits in favour of either nerandomilast or nintedanib, depending on the FVC endpoint chosen (see Section 2.10.4).[102] Clinical experts unanimously agreed that the available evidence supported equivalence in progression rates in lung decline.[93, 116] Additionally, the assumption of clinical similarity of pirfenidone and nintedanib is supported by independently published ITCs[117, 118], and prior acceptance of this assumption by NICE Committee in TA379.[18] The base case and scenario values for per cycle decline in FVC % predicted used are provided in Table 30. Scenarios explored transition probabilities for nintedanib and pirfenidone which are instead based on results from the ITCs (IPD meta-regression for nintedanib and/or NMA for pirfenidone), and the impact of adding a progression acceleration factor linked to acute exacerbations.

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Table 30: Per cycle FVC decline % used in the base case and scenario analysis for IPF

Scenario		Nerandomilast	Nintedanib	Pirfenidone	BSC
Base case	FVC % pred > 80	[redacted]	[redacted]	[redacted]	[redacted]
	FVC % pred < 80	[redacted]	[redacted]	[redacted]	[redacted]
NDB = IPD meta-regression	FVC % pred > 80	[redacted]	[redacted]	[redacted]	[redacted]
	FVC % pred < 80	[redacted]	[redacted]	[redacted]	[redacted]
PFN = NMA	FVC % pred > 80	[redacted]	[redacted]	[redacted]	[redacted]
	FVC % pred < 80	[redacted]	[redacted]	[redacted]	[redacted]
NDB = IPD meta-regression; PFN = NMA	FVC % pred > 80	[redacted]	[redacted]	[redacted]	[redacted]
	FVC % pred < 80	[redacted]	[redacted]	[redacted]	[redacted]
Increased risk following AcEx	FVC % pred > 80 no AcEx	[redacted]	[redacted]	[redacted]	[redacted]
	FVC % pred > 80 AcEx	[redacted]	[redacted]	[redacted]	[redacted]
	FVC % pred < 80 no AcEx	[redacted]	[redacted]	[redacted]	[redacted]
	FVC % pred < 80 AcEx	[redacted]	[redacted]	[redacted]	[redacted]

Key: AcEx, acute exacerbation; BSC, best supportive care; FVC, forced vital capacity; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; ITC, indirect treatment comparison; NDB, nintedanib; NMA, network meta-analysis; PFN, pirfenidone.

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3.3.2.2 PPF

The baseline FVC distribution in the 'no background AF therapy' cohorts of the FIBRONEER-ILD trial is presented in Table 31.[104]

Table 31: Baseline FVC distribution for PPF used in the model

FVC % predicted	FIBRONEER-ILD (N = 662)
≥ 110	[redacted]
100–109.9	[redacted]
90–99.9	[redacted]
80–89.9	[redacted]
70–79.9	[redacted]
60–69.9	[redacted]
50–59.9	[redacted]
40–49.9	[redacted]
30–39.9	[redacted]
Key: FVC, forced vital capacity; PPF, progressive pulmonary fibrosis.	

In the base case analysis, decline in FVC % predicted is modelled using constant transition rates derived from the FIBRONEER-ILD trial data. For nintedanib, these health-state transition rates are assumed to be the same as for nerandomilast. This assumption was made because the IPD meta-regression results did not show any clinically meaningful differences between the two treatments (see Section 2.10.4)[102], and clinical experts unanimously agreed that the available evidence supported equivalence in progression rates.[116] The rates of decline in FVC % predicted (per cycle) used in the base case and scenario analyses are provided in Table 32. Scenarios explored transition probabilities for nintedanib based on IPD meta-regression results and the impact of adding a progression acceleration factor linked to acute exacerbations.

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Table 32: Per cycle FVC % decline used in the base case and scenario analysis for PPF

Scenario		Nerandomilast	Nintedanib	BSC
Base case	FVC % pred > 70	[redacted]	[redacted]	[redacted]
	FVC % pred < 70	[redacted]	[redacted]	[redacted]
NDB = IPD meta-regression	FVC % pred > 70	[redacted]	[redacted]	[redacted]
	FVC % pred < 70	[redacted]	[redacted]	[redacted]
Increased risk following AcEx	FVC % pred > 70 no AcEx	[redacted]	[redacted]	[redacted]
	FVC % pred > 70 AcEx	[redacted]	[redacted]	[redacted]
	FVC % pred < 70 no AcEx	[redacted]	[redacted]	[redacted]
	FVC % pred < 70 AcEx	[redacted]	[redacted]	[redacted]

Key: AcEx, acute exacerbation; BSC, best supportive care; FVC, forced vital capacity; IPD, individual patient-level data; ITC, indirect treatment comparison; NDB, nintedanib; PPF, progressive pulmonary fibrosis.

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3.3.3 Risk of mortality

The follow-up period in the FIBRONEER trials is shorter than the full time horizon of the economic model, necessitating long-term extrapolation of survival data in line with NICE TSD 14.[119] Mortality transition probabilities were estimated using IPD for time to death from the FIBRONEER trials (nerandomilast and BSC) and IPD meta-regression (nintedanib, informed by INPULSIS/INBUILD). Access to IPD for both the nintedanib and nerandomilast trials is a unique advantage of this appraisal, enabling more robust mortality modelling and increasing confidence in the comparative treatment effect estimates compared with the aggregate data ITCs.

Joint parametric survival models were fitted to the time to death data to estimate cycle-specific probabilities of death. Seven standard parametric distributions were explored: exponential, Weibull (proportional hazards), Gompertz, gamma, log-normal, log-logistic, and generalised gamma (the latter did not converge for IPF). The analyses were conducted separately for IPF and PPF populations. Due to the relative immaturity of the mortality data, use of separately fitted survival models often led to implausible extrapolations, with the curves for nerandomilast and BSC crossing. This is contradictory to the clinically meaningful reductions in mortality observed for nerandomilast 18 mg bid monotherapy in both FIBRONEER trials (Sections 2.6.2 and 2.13.1). Therefore, analyses were restricted to joint models. The use of joint models including INPULSIS/INBUILD also preserves randomisation across the trials and so enables anchored comparisons between nerandomilast and nintedanib. Furthermore, as the proportional hazards (PH) assumption is considered to hold, the use of joint models is methodologically appropriate in this context.

Model selection followed a multi-step process consistent with TSD 14 guidance[119] and therefore:

- Tested the PH assumption to assess model suitability
- Compared models using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)
- Overlaid parametric curves on Kaplan–Meier plots for each treatment arm in IPF and PPF to assess visual alignment with observed trial data

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- Discussed the plausibility of extrapolations with UK clinical experts in ILD[93, 116] to ensure that long-term projections were consistent with clinical experience and expectations

Nerandomilast 18 mg bid led to nominally significant reductions compared with placebo in the risk of mortality in both FIBRONEER-IPF and FIBRONEER-PPF trials ('no AF background therapy' cohorts; see Section 2.6.2). Importantly, this represents the first time any RCT in IPF and PPF has shown such an effect, highlighting unprecedented and highly patient-relevant benefits of nerandomilast. In ITCs, nerandomilast also showed numerical reductions in mortality risk compared with both nintedanib and pirfenidone (see Section 2.10).

General population mortality data adjusted for age and gender (based on UK life tables) were used to ensure that, at each model cycle, the modelled risk of death was not lower than the risk of death in the general population.[133]

3.3.3.1 IPF

3.3.3.1.1 Summary of FIBRONEER-IPF survival data

Summary survival data from FIBRONEER-IPF are detailed in Table 33. Follow-up was [redacted] years and [redacted] years for nerandomilast and placebo, respectively. Over this period, three deaths were observed in the nerandomilast cohort, compared with 12 amongst patients randomised to placebo. OS data are shown in Kaplan–Meier graphs for nerandomilast, placebo and nintedanib in Figure 35 based on FIBRONEER-IPF and INPULSIS trial data.

Table 33: Summary of FIBRONEER-IPF survival data

	Nerandomilast	**Placebo**
N	87	87
Number of events	[redacted]	[redacted]
Follow-up (years)	[redacted]	[redacted]
RMST (years)	[redacted]	[redacted]
Key: N, number; RMST, restricted mean survival time.		

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Figure 35: Kaplan–Meier overall survival based on FIBRONEER-IPF (nerandomilast, placebo) and INPULSIS (nintedanib) data



Key: IPF, idiopathic pulmonary fibrosis; KM, Kaplan–Meier; Nera, nerandomilast; NDB, nintedanib.

3.3.3.1.2 Proportional hazards assessment

For both FIBRONEER-IPF and INPULSIS, the appropriateness of the PH assumption was assessed using the Schoenfeld residuals and log-cumulative hazard plots (see Appendix M). Some evidence for violation of the PH assumption was observed for the nintedanib arm. However, this was considered likely to be an artefact of the very small number of mortality events in FIBRONEER, rather than a true departure from proportionality, as low event counts can produce unstable estimates and false indications of non-proportionality. Due to the small number of events for nerandomilast and nintedanib, it was assumed that the PH assumption held; this ensured that resulting survival extrapolations were coherent (i.e. BSC

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never had higher OS than active treatment). This approach allowed treatment effects to be estimated directly, maintained internal validity, and aligned with clinical expectations for disease progression in IPF.

3.3.3.1.3 Visual and statistical assessment of fit

Table 34 summarises the goodness of fit for the parametric models to the observed data as assessed using AIC and BIC statistics. The joint parametric models and observed OS Kaplan–Meier data from FIBRONEER-IPF and INPULSIS trials are presented in Figure 36, Figure 37 and Figure 38. Landmark survival estimates for each treatment are presented in Table 35, Table 36, and Table 37.

The assessment of statistical and visual fit concluded that:

- Visual fit analysis in Figure 36, Figure 37 and Figure 38 showed that all models provide a similar fit to the Kaplan–Meier data
- The Gompertz model has the lowest AIC and BIC values, with the Weibull, log-logistic and gamma models having similar fit
- The generalised gamma distribution failed to converge and was excluded from consideration

Due to the visual similarity between the model fits and the relative immaturity of the mortality data (for example, only three IPF deaths were observed for nerandomilast 18 mg bid), no distributions were excluded solely on statistical grounds. Hence the clinical plausibility of all six parametric models was evaluated.

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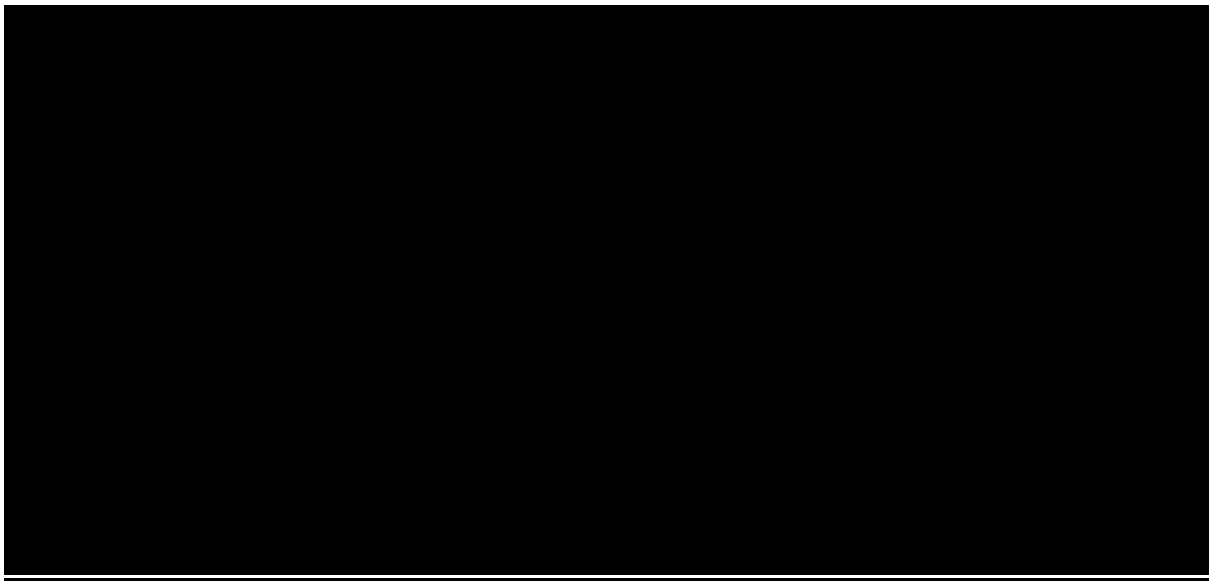
Table 34: Goodness of fit statistics for mortality in IPF

Distribution	AIC	BIC
Exponential (PH)	[redacted]	[redacted]
Weibull (PH)	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma*	–	–

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; IPF, idiopathic pulmonary fibrosis; PH, proportional hazards.
Notes: * Generalised gamma distribution was tested but failed to converge. **Bold text** represents the model with the best statistical fit

Figure 36: Short -term and long-term OS extrapolations for nerandomilast


[redacted]

Key: KM, Kaplan–Meier; OS, overall survival.

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Table 35: Landmark survival estimates for nerandomilast

Distribution	Years				
	1	2	5	10	20
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Note: The landmark survival estimates do not incorporate the treatment waning assumption					

Figure 37: Short-term and long-term OS extrapolations for placebo

[redacted]

Key: KM, Kaplan–Meier; OS, overall survival.

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Table 36: Landmark survival estimates for BSC

Distribution	Years				
	1	2	5	10	20
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: best supportive care.
Note: The landmark survival estimates do not incorporate the treatment waning assumption

Figure 38: Short-term and long-term OS extrapolations for nintedanib

[redacted]

Key: KM, Kaplan–Meier; OS, overall survival.

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Table 37: Landmark survival estimates for nintedanib

Distribution	Years				
	1	2	5	10	20
Weibull	[redacted]				
Exponential	[redacted]				
Gamma	[redacted]				
Log-logistic	[redacted]				
Log-normal	[redacted]				
Gompertz	[redacted]				
Note: The landmark survival estimates do not incorporate the treatment waning assumption					

3.3.3.1.4 Clinical expert opinion

For all three treatments, the gamma and Weibull models were considered the most plausible during independent validations with UK clinicians.[93, 116] Extrapolations from the Gompertz distribution were generally noted as being too pessimistic, albeit one clinician identified it as suitable for BSC mortality. Of the remaining survival models, the log-logistic was also identified as providing plausible estimates for nerandomilast (but not for nintedanib or BSC) by one clinician.

3.3.3.1.5 Conclusion

Based on the overall evidence, the gamma distribution was selected as the most clinically and statistically plausible choice for the base case analysis. While the Gompertz model produced the lowest AIC and BIC values, UK clinicians judged it to be overly pessimistic and unsuitable for most treatment arms. The gamma model was identified by clinicians as one of the best fitting models. In line with clinician feedback, scenario analyses were conducted using the Weibull and log-logistic distributions to assess the robustness of mortality estimates.

The relative treatment effect for nintedanib is applied as a HR calculated in the IPD meta-regression analysis (Section 2.10).[102] Access to IPD for nintedanib allowed for a robust statistical comparison to estimate a relative treatment effect of nerandomilast versus nintedanib.

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Given that IPD for pirfenidone were not available, and aggregate data ITC are likely biased (see Section 2.10.3.2), it was assumed that pirfenidone has equal OS to nintedanib. The assumption of similar clinical effectiveness is consistent with the decision in TA379 – in which the Committee accepted that the two AFs are clinically similar[18] – and was further validated by clinicians.[93, 116]

3.3.3.2 PPF

3.3.3.2.1 Summary of FIBRONEER-ILD survival data

Follow-up periods for the FIBRONEER-ILD trial were [redacted] years for nerandomilast and [redacted] years for placebo. A summary of survival data from FIBRONEER-ILD is detailed in Table 38. OS data are shown in Kaplan–Meier graphs for nerandomilast, placebo and nintedanib in Figure 39, based on FIBRONEER-ILD and INBUILD data.

Table 38: Summary of FIBRONEER-ILD survival data

	Nerandomilast	**Placebo**
N	220	222
Number of events	[redacted]	[redacted]
Follow-up (years)	[redacted]	[redacted]
RMST (years)	[redacted]	[redacted]
Key: N, number; RMST, restricted mean survival time.		

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Figure 39: Kaplan–Meier for overall survival based on FIBRONEER-ILD and INBUILD data



Key: KM, Kaplan–Meier; NDB, nintedanib; nera, nerandomilast.

3.3.3.2.2 Proportional hazards assessment

The appropriateness of the PH assumption was assessed using Schoenfeld residuals and log-cumulative hazard plots (see Appendix M). As with IPF, whilst there was potential evidence for a violation of the PH assumption, this was considered likely to be an artefact of the small number of mortality events in FIBRONEER, rather than a true departure from proportionality. Hence, consistent with the IPF analyses, joint survival models were estimated to ensure that consistent treatment effects were modelled.

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3.3.3.2.3 Visual and statistical assessment of fit

Table 39 summarises the goodness of fit for the parametric models to the observed data as assessed using AIC and BIC statistics. The joint parametric models and observed OS Kaplan–Meier data from the FIBRONEER-ILD and INBUILD trials are presented in Figure 40, Figure 41 and Figure 42. Landmark survival estimates for each treatment are presented in Table 40, Table 41 and Table 42.

The assessment of statistical and visual fit concluded that:

- Apart from the exponential and log-normal, all the distributions demonstrated a comparable visual and statistical fit during the trial period; however, there was a considerable uncertainty in the long-term extrapolations
- The exponential model provided a poor fit to the placebo and nintedanib arms, under-estimating survival for the majority of follow-up. The log-normal notably over-estimated survival for nerandomilast at the start of follow-up, followed by a notable under-estimation. These two distributions also had the worst fit based on AIC and BIC
- The Gompertz model had the lowest AIC and BIC values. All models apart from exponential, log-normal and generalised gamma had AIC and BIC values which were very similar to the Gompertz

Table 39: Goodness of fit statistics for mortality in PPF

Distribution	AIC	BIC
Exponential (PH)	[redacted]	[redacted]
Weibull (PH)	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PH, proportional hazards; PPF, progressive pulmonary fibrosis.
Note: Bold text represents the model with the best statistical fit.

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Figure 40: Short-term and long-term OS extrapolations for nerandomilast



Key: KM, Kaplan–Meier; OS, overall survival.

Table 40: Landmark survival estimates for nerandomilast

Distribution	Years				
	1	2	5	10	20
Weibull					
Exponential					
Gamma					
Log-logistic					
Log-normal					
Gompertz					
Note: The landmark survival estimates do not incorporate the treatment waning assumption					

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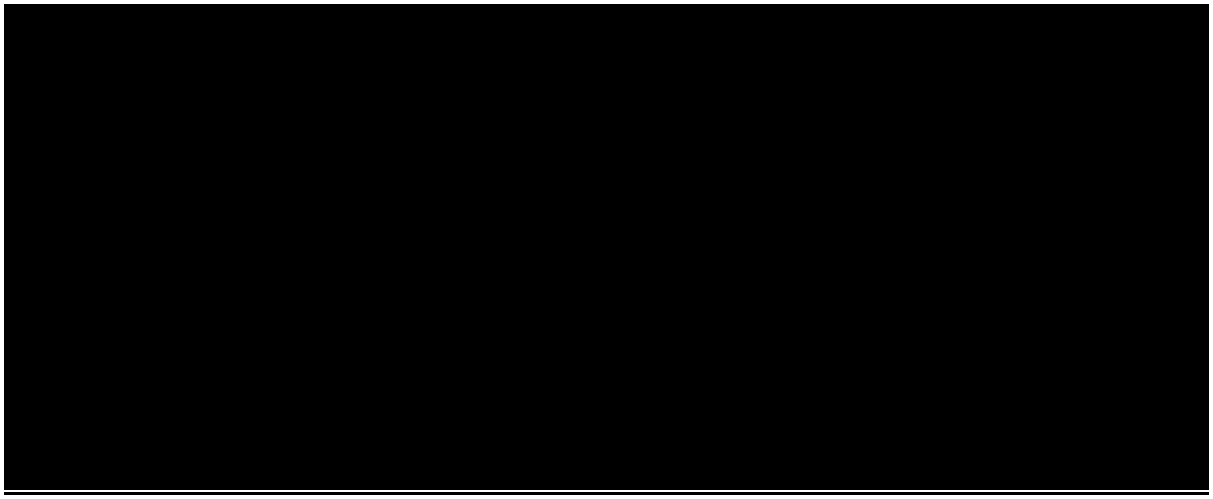
Figure 41: Short-term and long-term OS extrapolations for placebo



Key: KM, Kaplan–Meier; OS, overall survival.

Table 41: Landmark survival estimates for BSC

Distribution	Years				
	1	2	5	10	20
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care.
Note: The landmark survival estimates do not incorporate the treatment waning assumption

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Figure 42: Short-term and long-term OS extrapolations for nintedanib



Key: KM, Kaplan–Meier; OS, overall survival.

Table 42: Landmark survival estimates for nintedanib

Distribution	Years				
	1	2	5	10	20
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Note: The landmark survival estimates do not incorporate the treatment waning assumption					

3.3.3.2.4 Clinical expert opinion

As with IPF, expert clinical input was sought regarding the plausibility of the extrapolations from all the survival models. Feedback from clinical experts differed regarding the most appropriate fits for PPF. Respiratory specialists suggested that either the gamma or Weibull models were plausible (for all treatments), whereas rheumatologists preferred the more optimistic exponential and log-normal curves (again, for all treatments).[93] Rheumatologists reflected that the discrepancy may be linked to the type of patients they typically manage, mainly those with comorbid rheumatoid arthritis, who often experience a milder disease course and longer

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survival.[93] The Gompertz model was noted by all UK clinicians as being too pessimistic.[93] In separate validation interviews, respiratory specialists also noted that gamma and Weibull distributions provided the most plausible projections.[116]

3.3.3.2.5 Conclusion

After considering both statistical performance and clinical validation, the gamma distribution was chosen as the preferred option for the base case analysis. While the Gompertz delivered the lowest AIC and BIC scores, clinicians across the UK agreed that it produced overly pessimistic survival projections and was unsuitable for most treatment arms. Feedback from respiratory specialists supported the gamma or Weibull models as the most plausible models, whilst feedback from rheumatologists suggested that the exponential or log-normal models were the most plausible. Of these, the gamma was selected as it lies within 5 points of the best fitting model and is closer aligned to the rheumatologists' opinion. To explore the impact of alternative plausible curves noted by the rheumatologists, Weibull and log-normal models were incorporated into scenario analyses.

Similar to IPF, the model applies a relative treatment effect of nerandomilast versus nintedanib based on a HR calculated in the IPD meta-regression analysis, making best use of the available IPD for this comparison.

3.3.4 **Risk of acute exacerbation**

When a patient experiences an acute exacerbation, a short-term disutility value derived from pooled trial data is applied, and the per cycle cost is increased to reflect the additional resource use and healthcare burden during this period. These adjustments capture the temporary decline in quality of life and the increased economic impact associated with exacerbations. A scenario analysis is also conducted in which acute exacerbations influence transition probabilities, reflecting they may accelerate disease progression.

The approach to risk of acute exacerbation was consistent across IPF and PPF; as such, these are described together. There was no evidence to suggest a violation of the PH assumption for the time to first acute exacerbation; hence, joint models were deemed suitable and visually provided a good fit to the data. The joint models were

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fitted to pooled FIBRONEER and INPULSIS/INBUILD data, with treatment regimen as a predictor, consistent with the approach to modelling mortality, with further details provided in Appendix M.

The base case applies a constant risk of acute exacerbation per cycle in both IPF and PPF, differentiated only by treatment, which is in agreement with prior economic models in IPF/PPF (Table 43). The exponential distribution was chosen to extrapolate the risk of acute exacerbation over the model horizon because it provided the lowest AIC and BIC scores and were judged by clinical experts to be the most plausible.[93] This approach is also consistent with prior Markov models in IPF/PPF (see Section 3.1). The relative treatment effect of nerandomilast versus nintedanib is based on the IPD meta-regression; for pirfenidone, efficacy was assumed to be equal to nintedanib.

Scenario analyses were conducted whereby acute exacerbation rates were equal to the nerandomilast rate across all treatments for robustness and where acute exacerbation risk increases as FVC % predicted decreases (in addition to being dependent on treatment received; Table 44). The latter analysis was conducted because clinical experts consulted during model conceptualisation indicated that the risk of acute exacerbation is likely to increase with disease severity.[93]

Table 43: Constant risks of acute exacerbation by treatment for IPF and PPF

Scenario	Nerandomilast	Nintedanib	BSC	Pirfenidone
IPF				
Base case	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: all active treatments equal to Nera	[redacted]	[redacted]	[redacted]	[redacted]
PPF				
Base case	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: all treatments equal to Nera	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; IPF, idiopathic pulmonary fibrosis; Nera, nerandomilast; PPF, progressive pulmonary fibrosis.

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Table 44: Risk of acute exacerbation varied by FVC % predicted by treatment for IPF and PPF

Scenario	Nerandomilast	Nintedanib	BSC	Pirfenidone
IPF				
≥ 110	[redacted]	[redacted]	[redacted]	[redacted]
100–109.9	[redacted]	[redacted]	[redacted]	[redacted]
90–99.9	[redacted]	[redacted]	[redacted]	[redacted]
80–89.9	[redacted]	[redacted]	[redacted]	[redacted]
70–79.9	[redacted]	[redacted]	[redacted]	[redacted]
60–69.9	[redacted]	[redacted]	[redacted]	[redacted]
50–59.9	[redacted]	[redacted]	[redacted]	[redacted]
40–49.9	[redacted]	[redacted]	[redacted]	[redacted]
30–39.9	[redacted]	[redacted]	[redacted]	[redacted]
PPF				
≥ 110	[redacted]	[redacted]	[redacted]	[redacted]
100–109.9	[redacted]	[redacted]	[redacted]	[redacted]
90–99.9	[redacted]	[redacted]	[redacted]	[redacted]
80–89.9	[redacted]	[redacted]	[redacted]	[redacted]
70–79.9	[redacted]	[redacted]	[redacted]	[redacted]
60–69.9	[redacted]	[redacted]	[redacted]	[redacted]
50–59.9	[redacted]	[redacted]	[redacted]	[redacted]
40–49.9	[redacted]	[redacted]	[redacted]	[redacted]
30–39.9	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.

Repeated acute exacerbations are not tracked separately; thus, the model does not differentiate the impact of the number of acute exacerbations on the risk of progression, mortality and supplemental oxygen need. This is due to the limited data available to differentiate the impact of the first acute exacerbation versus subsequent acute exacerbations. Nevertheless, based on clinical experts' consultations, it is rare for patients to have multiple acute exacerbations, since patients never fully recover from an acute exacerbation, and it is therefore difficult to define when one acute exacerbation ends and another begins.[116]

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3.3.5 Treatment discontinuation

Discussion with clinical experts highlighted that the availability of nerandomilast monotherapy might lead to more complex treatment sequences, with at least some of the patients discontinuing nerandomilast potentially receiving an AF before BSC, while AF discontinuers were likely to receive nerandomilast before BSC.[116] Treatment sequences are not captured in the model, given the increased model complexity required and the lack of data available to characterise the impact of nerandomilast exposure on AF effectiveness, along with nerandomilast effectiveness post-AF exposure. Hence, as a simplifying approach it is assumed that patients receiving nerandomilast or currently available AF move on to BSC (costs and efficacy) after treatment discontinuation.

The base case assumes a constant rate of discontinuation, based on the exponential distribution providing both acceptable fit to the observed data and plausible extrapolations. Scenario analyses were conducted for both IPF and PPF using a parametric-based discontinuation approach to explore the impact of a non-constant discontinuation rate as per clinical feedback.[93] The choice of survival curve for TTD followed the same multi-step process outlined in Section 3.3.3. Full details on this are provided in Appendix M. The selected curves are outlined in Section 3.3.5.1.3 for IPF and Section 3.3.5.2.3 for PPF.

A stopping rule is also applied to all active treatments if the patient experiences a drop of FVC % predicted greater than 10%. This aligns with the formal guidelines for nintedanib in IPF, but clinical experts noted that this stopping rule typically applies in practice across both disease areas for all active treatments.[93] A scenario also explored the impact of nerandomilast being the only treatment to have a formal stopping rule.

To ensure the model fully reflects the benefits observed throughout the clinical trial period, the treatment effects of active treatments are maintained for one year after the maximum follow-up duration of the FIBRONEER trials, regardless of whether a patient discontinues treatment, in line comments from the Evidence Assessment Group (EAG) in TA747.[47] This is because patients who discontinue are not censored from the efficacy analyses in the FIBRONEER trials or IPD meta-regression.

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Therefore, the base case analysis assumes the treatment effect may last until [redacted] years from treatment initiation in the IPF population and [redacted] years in the PPF population (based on the respective FIBRONEER trials follow-up with an additional year of protective treatment effect) before patients who have discontinued active treatment revert to BSC transition probabilities. An additional scenario assuming the treatment effect for each population is protected for only the maximum follow-up of the FIBRONEER trials was analysed to assess the impact of this assumption.

3.3.5.1 IPF

3.3.5.1.1 Summary of trial discontinuation data

Based on a consideration of the available curves, the exponential distribution was chosen as providing both acceptable fit to the observed data and plausible extrapolations. Specifically, it provided similar within-sample fit to the other models and was the only one that did not require capping by general population mortality at 20 years. Hence, a constant treatment discontinuation rate per model cycle was applied. The constant hazard approach assumes the probability of discontinuation remains constant over time.

Estimates for nerandomilast and nintedanib were derived from a statistical analysis of pooled data from the FIBRONEER-IPF (DBL2) and INPULSIS trials, using all the available data. These trial-derived estimates were considered the most internally valid measures of early discontinuation, as they reflect directly observed data under standardised trial follow-up conditions. Based on clinical opinion, rates of discontinuation for pirfenidone were assumed equal to those for nintedanib. Observed Kaplan–Meier curves for each comparator are displayed in Figure 43.

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Figure 43: Observed Kaplan–Meier curves for TTD in the IPF cohort



Key: IPF, idiopathic pulmonary fibrosis; KM, Kaplan–Meier; NDB, nintedanib; NERA, nerandomilast; TTD, time to treatment discontinuation.
Notes: NDB follow-up reflective of INPULSIS trial.

3.3.5.1.2 Base case discontinuation rates

The discontinuation rates used in the model base case are presented in Table 45, with the proportion of patients remaining on treatment each year presented in Figure 44.

Table 45: Discontinuation rates used in the model base case – IPF

Treatment	Discontinuation rate per cycle	Low 95% CI	High 95% CI
Nerandomilast	[redacted]	[redacted]	[redacted]
Nintedanib	[redacted]	[redacted]	[redacted]
Pirfenidone*	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; IPF, idiopathic pulmonary fibrosis.
Notes: *Pirfenidone assumed equal to nintedanib.

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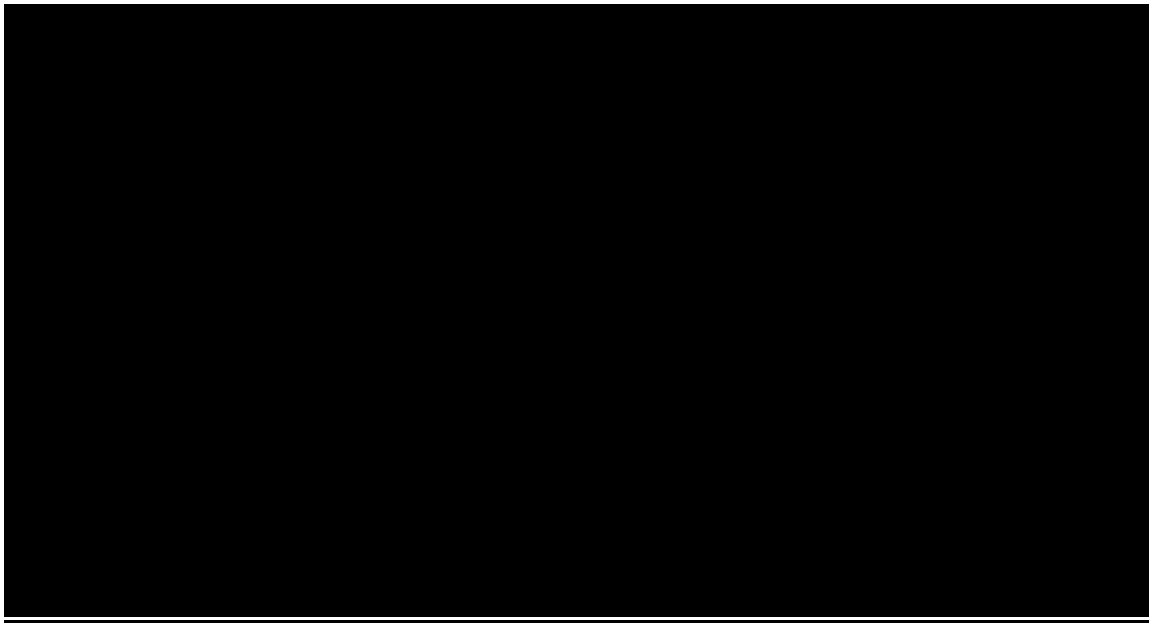
Figure 44: TTD in the model base case – IPF



Key: IPF, idiopathic pulmonary fibrosis; NDB, nintedanib; NERA, nerandomilast; TTD, time to treatment discontinuation.
Notes: PFN assumed equal to NDB.

Changes in treatment efficacy following discontinuation only occur after 52 weeks (four model cycles). This aligns with the primary outcome time point for FIBRONEER-IPF, as the impact of discontinuation on efficacy will already be reflected within the trial outcomes so any further adjustment would be double-counting. After 52 weeks all clinical outcomes (risk of FVC % predicted progression, risk of acute exacerbation, risk of death) are based on BSC-specific efficacy inputs.

3.3.5.1.3 Clinical expert opinion

Projections for longer-term TTD, such as at 5 years, were considered reasonable, but uncertain.[93] To address that uncertainty, an alternative scenario utilising standard parametric extrapolations was explored using the Gompertz model for the nerandomilast arm and exponential model for nintedanib arm (Appendix M for detail).

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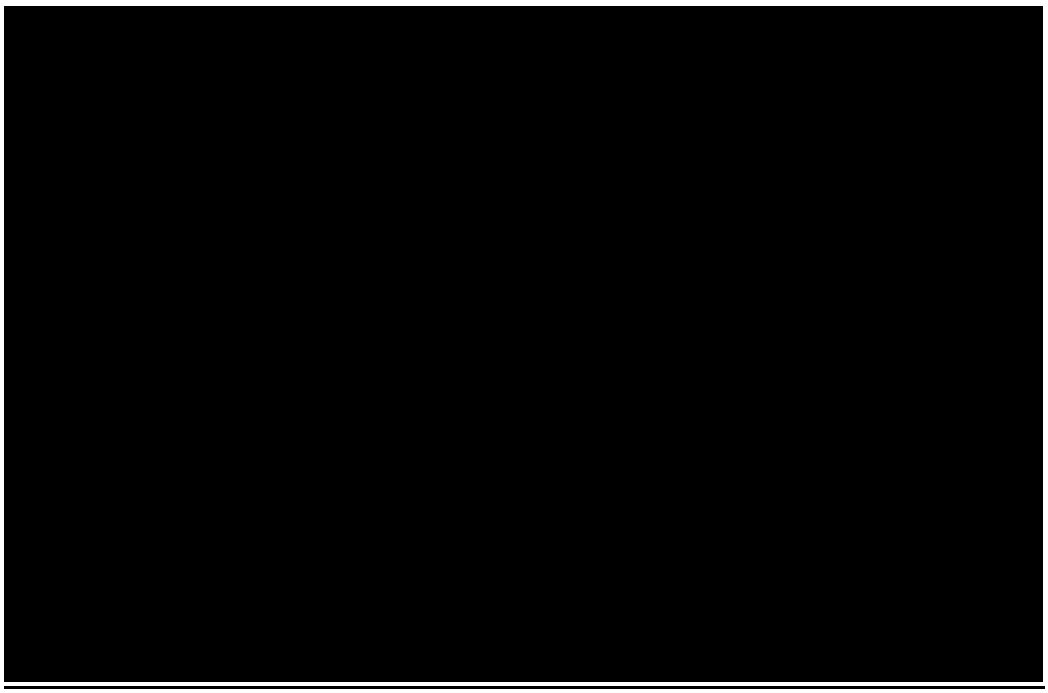
3.3.5.2 PPF

3.3.5.2.1 Summary of trial discontinuation data

As with IPF, based on a consideration of the available curves, the exponential distribution was chosen as providing both acceptable fit to the observed data and plausible extrapolations. Specifically, it provided the best within-sample fit based on BIC and second-best based on AIC, and extrapolations did not require capping by general population mortality. Hence, a constant treatment discontinuation rate per model cycle was applied. The constant hazard approach assumes the probability of discontinuation remains constant over time.

Estimates for nerandomilast and nintedanib were derived from a statistical analysis of pooled data from the FIBRONEER-ILD (DBL2) and INBUILD trials, using all the available data. These trial-derived estimates were considered the most internally valid measures of early discontinuation, as they reflect directly observed data under standardised trial follow-up conditions. Observed Kaplan–Meier curves for each comparator are displayed in Figure 45.

Figure 45: Observed Kaplan–Meier curves for TTD in the PPF cohort



Key: KM, Kaplan–Meier; NDB, nintedanib; NERA, nerandomilast; PPF, progressive pulmonary fibrosis; TTD, time to treatment discontinuation.

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3.3.5.2.2 Base case discontinuation rates

The discontinuation rates used in the model base case are presented in Table 46, with the proportion of patients remaining on treatment each year presented in Figure 46.

Table 46: Discontinuation rates used in the model base case – PPF

Treatment	Discontinuation rate per cycle	Low 95% CI	High 95% CI
Nerandomilast	[redacted]	[redacted]	[redacted]
Nintedanib	[redacted]	[redacted]	[redacted]
Key: CI, confidence interval; PPF, progressive pulmonary fibrosis.			

Figure 46: TTD extrapolations used in the model base case – PPF



Key: NDB, nintedanib; NERA, nerandomilast; PPF, progressive pulmonary fibrosis; TTD, time to treatment discontinuation.

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Changes in treatment efficacy following discontinuation only occur after 52 weeks (four model cycles). This aligns with the primary outcome time point for FIBRONEER-ILD, as the impact of discontinuation on efficacy will already be reflected within the trial outcomes so any further adjustment would be double-counting. After 52 weeks all clinical outcomes (risk of FVC % predicted progression, risk of acute exacerbation, risk of death) are based on BSC-specific efficacy inputs.

3.3.5.2.3 Clinical expert opinion

Projections for longer-term TTD, such as at 5 years, were considered reasonable, but uncertain.[93] To address that uncertainty, an alternative scenario utilising standard parametric extrapolations was explored using the exponential model for the nerandomilast arm and Weibull model for nintedanib arm (Appendix M for detail).

3.3.6 Safety

The following AEs were included in the model:

- Severe (Grade 3+) AEs with a frequency of 5% or higher in the nerandomilast arms of the FIBRONEER trials (Section 2.11)
- AEs of Grade 3+ that were included in previous NICE TAs for IPF and PPF[47, 51, 80]

According to the criteria above, the only difference is that the AE 'photosensitivity reaction' was included for IPF but not PPF. AE frequencies were sourced from FIBRONEER-IPF (no background AF therapy cohort), INPULSIS (nintedanib), and CAPACITY (pirfenidone) trial data for IPF, and FIBRONEER-ILD (no background AF therapy cohort) and INBUILD (nintedanib) trial data for PPF (Table 47).[103, 104, 123, 129-131]

Table 47: Frequencies of Grade 3+ adverse events

	IPF				PPF		
Treatment	**NERA[a]**	**BSC[a]**	**NDB[b]**	**PFN[c]**	**NERA[a]**	**BSC[a]**	**NDB[b]**
N patients	87	87	638	345	220	222	332
Cardiac events	[redacted]	[redacted]	5.0%	7.2%	[redacted]	[redacted]	6.6%
Pneumonia	[redacted]	[redacted]	3.6%	1.4%	[redacted]	[redacted]	9.4%
Diarrhoea	[redacted]	[redacted]	3.4%	3.5%	[redacted]	[redacted]	1.9%

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	IPF				PPF		
Treatment	**NERA[a]**	**BSC[a]**	**NDB[b]**	**PFN[c]**	**NERA[a]**	**BSC[a]**	**NDB[b]**
GI disorders (without diarrhoea)	[redacted]	[redacted]	0.0%	0.8%	[redacted]	[redacted]	2.8%
Photosensitivity reaction	[redacted]	[redacted]	0.0%	2.3%	NA	NA	NA

Key: AE, adverse event; AF, antifibrotic; BSC, best supportive care; GI, gastrointestinal; IPF, idiopathic pulmonary fibrosis; N, number; NA, not applicable; NDB, nintedanib; NERA, nerandomilast; PFN, pirfenidone; PPF, progressive pulmonary fibrosis.
Notes: AE frequencies based on: [a] FIBRONEER trials (no background AF therapy cohorts)[103, 104], [b] INPULSIS/INBUILD[123, 129], [c] CAPACITY.[130, 131]

Given that AEs typically occur more often in the initial stages of treatment, the model provides the option to either accrue all AE costs upon treatment initiation (i.e. one-off frontloading approach) or to distribute them evenly during treatment (i.e. constant probability approach). In the base case, the AE costs are applied as a one-off cost upon treatment initiation. This approach has been used and supported in previous submissions in this area.[47, 51, 80]

3.3.7 Summary of clinical inputs and approaches

A summary of the options included for modelling the clinical parameters is included in Table 48. The base case settings are highlighted in blue; the rationale for the base case settings and scenarios can be found in the relevant sections referred to in the table.

Table 48: Summary of base case and scenario approaches

Option	Description	Relevant section
Change in FVC over time		
Nerandomilast, nintedanib and pirfenidone all have equal risk of progression (constant over time; regardless of acute exacerbation history) (base case)	A different risk of FVC % predicted decline is used in the analysis for FVC % predicted health states above or below a threshold of 80 (for IPF) and above or below 70 for PPF. Based on non-significant ITC results and clinical discussion, this is equivalent across nerandomilast and the AF treatments	Section 3.3.2
Nintedanib risk of progression equal to ITC	FVC % predicted for nintedanib now equal to IPD meta-regression rather than equal to nerandomilast	

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Option	Description	Relevant section
Pirfenidone risk of progression equal to ITC (IPF only)	FVC % predicted for pirfenidone now equal to NMA rather than equal to nerandomilast	
Nintedanib and pirfenidone risk of progression equal to ITC (IPF only)	FVC % predicted equal to IPD meta-regression (nintedanib) and Bayesian NMA (pirfenidone) rather than equal to nerandomilast	
Different risk of progression by history of acute exacerbation	A different risk of FVC % predicted decline differentiating based on history of acute exacerbation*	
Risk of mortality		
Treatment-based survival analysis – Gamma (base case)	The risk of death is only dependent on the treatment received. This is aligned with previous cost-effectiveness models submitted to NICE in this disease area, which have all been accepted.[47, 51, 80] Based on clinical validation and statistical analyses, the model used a joint Gamma model in the base case.	Section 3.3.3
Treatment-based survival analysis – Weibull	Based on clinical validations, this was noted as a model that provided plausible extrapolations, so was explored in scenario analysis	
Treatment-based survival analysis – log-logistic (IPF) and log-normal (PPF)	Based on clinical validations, this was noted as a model that provided plausible extrapolations, so was explored in scenario analysis	
Risk of acute exacerbation		
Constant risk of acute exacerbation across FVC % predicted health states (base case)	A constant risk of acute exacerbation is used in the analysis, only differentiated by treatment	Section 3.3.4
Acute exacerbation rates to be equal across nerandomilast and active AF treatments	Acute exacerbation rates for nerandomilast defined using FIBRONEER data and applied to all treatments	
Different risk of acute exacerbation by FVC % predicted health states	A different risk of acute exacerbation is used in the analysis for FVC % predicted health states. The treatment effect is constant and not differentiated by FVC % predicted health states	
Treatment discontinuation		
Constant per cycle discontinuation rate applied per treatment with stopping rule applied to all treatments (base case)	A constant per cycle discontinuation rate is used in the analysis, only differentiated by treatment. Stopping rule is applied to all active treatments for > 10% FVC % predicted decline, aligned with stopping rule in TA379[18] and TA504[51]	Section 3.3.5

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Option	Description	Relevant section
Treatment discontinuation based on best fitting parametric extrapolations	The best fitting parametric extrapolations for nerandomilast and nintedanib (IPF: nerandomilast, Gompertz; nintedanib, exponential. PPF: nerandomilast, exponential; nintedanib, Weibull) are applied to model treatment discontinuation based on the approach in Appendix M	
Stopping rule applied to nerandomilast only	A stopping rule is applied to nerandomilast only for > 10% FVC % predicted decline	
Treatment effect waning for all active treatments	FVC progression and mortality do not equal BSC progression and mortality until [redacted] years after treatment initiation in the IPF population and [redacted] years after discontinuation in the PPF population	
Safety		
Grade 3+ AEs applied as one-off cost (base case)	Grade 3+ AEs are applied in Cycle 1 of the model as a one-off cost	Section 3.3.6

Key: AE, adverse event; AF, antifibrotics; FVC, forced vital capacity; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; ITC, indirect treatment comparison; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PPF, progressive pulmonary fibrosis.
Notes: Shaded blue indicates the option included in the base case. * The treatment effect is constant and not differentiated by FVC % predicted health states or history of acute exacerbation. The acceleration factor for FVC % predicted decline post-acute exacerbation is derived from external sources.

3.4 Measurement and valuation of health effects

The model incorporates the important impact of IPF and PPF on HRQL based on disease progression status and the impact of acute exacerbations and AEs due to treatment. A health state utility approach is used in the base case, assigning a health state utility value to capture the patient's HRQL based on their FVC % predicted status. Additionally, HRQL decrements due to both AEs and ageing were considered in line with the NICE reference case. Short-term disutilities related to acute exacerbations were also accounted for in the model.

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3.4.1 Health-related quality of life data from clinical trials

3.4.1.1 IPF

For the base case analysis in IPF, baseline health state utility values were sourced from the statistical analysis of pooled INPULSIS and FIBRONEER-IPF trial data. EQ-5D data, collected longitudinally, were analysed using generalised linear mixed models (GLMM) with random patient intercepts. Results of the utility analyses for the IPF population are displayed in Table 49. Utility values per health state are provided in Table 50. Full statistical analysis can be found in Appendix M. Utilities are assumed to be equal for all FVC % predicted categories above 80 as there are limited patient numbers above this level. Additionally, a regression model using more granular categories provided inconsistent results.

Table 49: Utility analyses results in the IPF population

Term	Estimate	SE
Intercept	[redacted]	[redacted]
Baseline utility	[redacted]	[redacted]
FVC % Pred: 40–49.9	[redacted]	[redacted]
FVC % Pred: 50–59.9	[redacted]	[redacted]
FVC % Pred: 60–69.9	[redacted]	[redacted]
FVC % Pred: 70–79.9	[redacted]	[redacted]
FVC % Pred: 80+	[redacted]	[redacted]
Last AcEx ≤ 30 days	[redacted]	[redacted]
Last AcEx ≥ 31 days	[redacted]	[redacted]

Key: AcEx, acute exacerbation; FVC % Pred, forced vital capacity percent predicted; IPF, idiopathic pulmonary fibrosis; SE, standard error.
Notes: Last AcEx variables are categorical time-varying predictors with 0 as the reference category.

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Table 50: Health state utilities in IPF

FVC % predicted	Utility value	Notes
≥ 110	[redacted]	Utilities are assumed to be equal for all FVC % predicted categories above 80
100–109.9	[redacted]	
90–99.9	[redacted]	
80–89.9	[redacted]	
70–79.9	[redacted]	
60–69.9	[redacted]	
50–59.9	[redacted]	
40–49.9	[redacted]	
30–39.9	[redacted]	

Key: DBL, data base lock; DSA, deterministic sensitivity analysis; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; PSA, probabilistic sensitivity analysis.
Notes: Standard errors are not used if trial-based data are selected; DSA and PSA use regression model coefficients and variance–covariance matrix.
Source: Statistical analysis of pooled INPULSIS and FIBRONEER-IPF DBL2 data.

3.4.1.2 PPF

For the base case analysis, baseline health state utility values were sourced from the statistical analysis of pooled INBUILD and FIBRONEER-ILD trial data for PPF. EQ-5D data, collected longitudinally, were analysed using GLMM with random patient intercepts. Results of the utility analyses for the PPF population are displayed in Table 51. Trial specific utility values are provided within Table 52. Full statistical analysis can be found in Appendix M. Utilities are assumed to be equal for all FVC % predicted categories above 80 as there are limited patient numbers above this level. Additionally, a regression model using more granular categories provided inconsistent results.

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Table 51: Utility analyses results in the PPF population

Term	Estimate	SE
Intercept	[redacted]	[redacted]
Baseline utility	[redacted]	[redacted]
FVC % Pred: 40–49.9	[redacted]	[redacted]
FVC % Pred: 50–59.9	[redacted]	[redacted]
FVC % Pred: 60–69.9	[redacted]	[redacted]
FVC % Pred: 70–79.9	[redacted]	[redacted]
FVC % Pred: 80+	[redacted]	[redacted]
Last AcEx ≤ 30 days	[redacted]	[redacted]
Last AcEx ≥ 31 days	[redacted]	[redacted]

Key: AcEx, acute exacerbation; FVC % Pred, forced vital capacity percent predicted; PPF, progressive pulmonary fibrosis; SE, standard error.
Notes: Last AcEx variables are categorical time-varying predictors with 0 as the reference category.

Table 52: Trial-based health state utilities in PPF

FVC % predicted	Utility value	Notes
≥ 110	[redacted]	Utilities are assumed to be the same for all FVC % predicted categories above 80
100–109.9	[redacted]	
90–99.9	[redacted]	
80–89.9	[redacted]	
70–79.9	[redacted]	
60–69.9	[redacted]	
50–59.9	[redacted]	
40–49.9	[redacted]	
30–39.9	[redacted]	

Key: AF, antifibrotics; DBL, data base lock; DSA, deterministic sensitivity analysis; FVC, forced vital capacity; PPF, progressive pulmonary fibrosis; PSA, probabilistic sensitivity analysis.
Notes: Standard errors are not used if trial-based data are selected; DSA and PSA use regression model coefficients and variance–covariance matrix.
Source: Calculated from DBL2 of FIBRONEER-ILD and Final DBL from INBUILD, Non-AF Cohort, 22 July 2025.

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3.4.2 Mapping

In accordance with NICE's guidance[128], the EQ-5D-5L questionnaires collected in the FIBRONEER trials were mapped onto the 3L value set using the mapping function developed by the NICE Decision Support Unit.[120]

3.4.3 Health-related quality of life studies

An SLR was conducted to identify studies for utility and HRQL in IPF and PPF. Searches were run in September 2025.[134] In total, 148 studies from 151 publications were included within the review. Full details of the review are provided in Appendix E and in the SLR report provided in the reference pack.[134] Key sources identified by the review include Rinciog et al. 2017 which uses utility values from INPULSIS in IPF, and utility values from INBUILD obtained from NICE TA747.[47, 123]

3.4.4 Acute exacerbations

The model applies a short-term disutility during acute exacerbations for both IPF and PPF. For IPF, a disutility value of [redacted] is applied, derived from pooled INPULSIS final DBL and FIBRONEER-IPF DBL2 data.[108] For PPF, a disutility value of [redacted] is applied, derived from pooled INBUILD final DBL and FIBRONEER-ILD DBL2 data.[109] It is anticipated that the long-term impact of acute exacerbations is already captured in the health state estimates derived from trial data. To address clinical expert's concerns regarding high utilities after acute exacerbation, a scenario analysis explores values from INPULSIS alone as these provide lower estimates.[93] IPF-specific values are shown in Table 53.

Table 53: Summary of disutility values for acute exacerbation in IPF

Source	Value
Pooled FIBRONEER-IPF/INPULSIS[101]	[redacted]
INPULSIS[123]	0.1400
Key: IPF, idiopathic pulmonary fibrosis.	

For PPF, a disutility value of 0.1340 is applied, derived from pooled INBUILD final DBL and FIBRONEER-ILD DBL2 data.[109] To address clinical expert's concerns with high utilities, a scenario analysis explores values from INBUILD alone based on TA747 data as these utilities are lower.[47, 93, 116] PPF-specific values are shown in Table 54.

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Table 54: Disutility of acute exacerbation in PPF used in model

Source	Value
Pooled FIBRONEER-ILD/INBUILD[101]	[redacted]
INBUILD[47]	0.1668
Key: PPF, progressive pulmonary fibrosis.	

It is anticipated that the long-term impact of acute exacerbations is already captured in the health state estimates derived from trial data.

3.4.5 Adverse reactions

AE-related disutilities were considered in the analysis for the proportion of patients experiencing Grade 3+ AEs as detailed in Section 3.3.6.

Disutility values for pneumonia were sourced from Sullivan et al. 2011[135] using the values reported for 'other lung disease', in line with NICE TA599.[136] All other disutilities are as reported in TA864[80]: episodes of diarrhoea and GI disorders (assumed equal to those for diarrhoea) are based on Rinciog et al. 2017.[123] Ara and Brazier, 2011[137] provided the source for disutility values for photosensitivity reactions and cardiac events.

All sourced disutility values are scaled down to weekly disutility values and are summarised in Table 55. The duration of disutilities is assumed to be one model cycle, consistent with previous appraisals. The total AE-related utility decrement per treatment arm is presented in Table 56.

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Table 55: AE-related disutility

AE	Weekly disutility value	SE	Disutility duration (weeks)	Source
Cardiac events	0.0038	0.0008	4.35	TA864; Ara and Brazier, 2011[80, 137]
Pneumonia	0.0388	0.0078	4.35	TA599; Sullivan et al., 2011[136]
Diarrhoea	0.0002	0.0000	4.35	TA864; Rinciog et al., 2017[80, 123]; assume half of a serious GI event disutility, based on post hoc analysis of INPULSIS safety data
GI disorders (without diarrhoea)	0.0002	0.0000	4.35	TA864; Rinciog, 2017[80, 123]
Photosensitivity reaction	0.0004	0.0001	4.35	TA864; Ara and Brazier, 2011[80, 137]

Key: AE, adverse event; GI, gastrointestinal; SE, standard error; TA, technology appraisal.
Notes: Duration is an assumption; SE is 20% of mean value. Diarrhoea disutility values assume half of GI event disutility, based on post hoc analysis of INPULSIS safety data. Disutility value for GI disorders assumed equal to the one reported for diarrhoea.

Table 56: Total AE-related utility decrement per treatment arm

Indication	Nerandomilast	Nintedanib	BSC	Pirfenidone
IPF	0.0066	0.0069	0.0126	0.0037
PPF	0.0164	0.0170	0.0175	NA

Key: AE, adverse event; BSC, best supportive care; IPF, idiopathic pulmonary fibrosis; NA, not applicable; PPF, progressive pulmonary fibrosis.

3.4.6 Disutility of liver function tests

While the disutility value of liver function monitoring is small, it represents a real burden to patients which is not captured by trial-derived health state utility values. In routine practice, liver function monitoring can involve travel, waiting times, minor physical discomfort, and anxiety while awaiting results. These process-related impacts are generally absent from RCT settings, where patients often receive enhanced support and monitoring as part of study protocols.

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No published evidence was identified that directly quantified a disutility associated with diagnostic testing. In the absence of a testing specific value, the disutility applied in this model is assumed to be the same as that reported for an intravenous (IV) infusion in TA898. The input used in TA898 includes the disutility of three infusions, but this has been adjusted to a single infusion (0.008).[138] This assumption is considered reasonable as the IV infusion disutility captures similar elements that contribute to the burden of liver function monitoring. Applying this decrement ensures that the relevant disutility value of repeated monitoring is reflected in the model. For more details on the frequencies of liver function monitoring, see Section 3.5.1.2.

3.4.7 Health-related quality of life data used in the cost-effectiveness analysis

3.4.7.1 IPF

HRQL inputs for the economic model were primarily derived from the pooled patient-level EQ-5D data presented in Section 3.4.1.1. Health state utility values were also adjusted for age and sex using the UK EQ-5D-3L general population norms based on Hernandez Alava et al. 2022 with values capped by general population utility presented in Table 57.[120] As a scenario, utility data from Rinciog et al. 2017 were used, as presented in Table 58.[123]

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Table 57: Trial-based health state utilities capped by general population values in IPF

FVC % predicted	Utility value	Note
≥ 110	[redacted]	Trial-predicted utility values were greater than those for the general population for FVC % predicted ≥ 80. Hence, general population utility values were used for FVC % predicted ≥ 80, with the remaining FVC-specific utilities derived by applying FVC-specific decrements as estimated from FIBRONEER-IPF/INPULSIS pooled data. This approach ensures that deteriorating lung function corresponds to decreasing utility values
100–109.9	[redacted]	
90–99.9	[redacted]	
80–89.9	[redacted]	
70–79.9	[redacted]	
60–69.9	[redacted]	
50–59.9	[redacted]	
40–49.9	[redacted]	
30–39.9	[redacted]	

Key: FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.
Source: FIBRONEER-IPF/INPULSIS pooled data.[101]

Table 58: Health state utilities from INPULSIS in IPF

FVC % predicted	Utility value	SE	Note
≥ 110	0.8380	0.1676	Assumed as the same as for FVC % predicted 90–99.9
100–109.9	0.8380	0.1676	Assumed as the same as for FVC % predicted 90–99.9
90–99.9	0.8380	0.1676	
80–89.9	0.8105	0.1621	
70–79.9	0.7800	0.1560	
60–69.9	0.7657	0.1531	
50–59.9	0.7387	0.1477	
40–49.9	0.6634	0.1327	
30–39.9	0.6634	0.1327	Assumed as the same as for FVC % predicted 40–49.9

Key: FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; SE, standard error.
Notes: SEs are calculated as 20% of mean values.
Source: Post hoc analysis of INPULSIS data (Rinciog, 2017).[123]

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3.4.7.2 PPF

HRQL inputs for the economic model were primarily derived from the pooled patient-level EQ-5D data presented in Section 3.4.1.2. Health state utility values were also adjusted for age and sex using the UK EQ-5D-3L general population norms based on Hernandez Alava et al. 2022.[120] Values capped by general population utility are presented in Table 59. As a scenario, utility data from TA747 were used, as presented in Table 60.[47]

Table 59: Trial-based health state utilities capped by general population values in PPF

FVC % predicted	Utility value no AF	Note
≥ 110	[redacted]	Trial-predicted utility values were greater than those for the general population for FVC % predicted ≥ 80. Hence, general population utility values were used for FVC % predicted ≥ 80, with the remaining FVC-specific utilities derived by applying FVC-specific decrements as estimated from FIBRONEER-ILD/INBUILD pooled data. This approach ensures that deteriorating lung function corresponds to decreasing utility values
100–109.9	[redacted]	
90–99.9	[redacted]	
80–89.9	[redacted]	
70–79.9	[redacted]	
60–69.9	[redacted]	
50–59.9	[redacted]	
40–49.9	[redacted]	
30–39.9	[redacted]	

Key: AF, antifibrotic; FVC, forced vital capacity; PPF, progressive pulmonary fibrosis.
Source: FIBRONEER-ILD/INBUILD.[101]

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Table 60: Health state utilities from INBUILD in PPF

FVC % predicted	Utility value	SE	Notes
≥ 110	0.7521	0.0076	
100–109.9	0.7521	0.0076	
90–99.9	0.7287	0.0068	
80–89.9	0.7333	0.0061	
70–79.9	0.7242	0.0063	
60–69.9	0.6750	0.0070	
50–59.9	0.6453	0.0067	
40–49.9	0.6045	0.0073	
30–39.9	0.6045	0.0073	Assumed the same as for FVC % predicted 40–49.9

Key: FVC, forced vital capacity; NICE, National Institute for Health and Care Excellence; PPF, progressive pulmonary fibrosis; SD, standard deviation; SE, standard error; TA, technology appraisal.
Notes: SEs were calculated as SD divided by square root of overall sample size.
Source: NICE TA747.[47]

3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify relevant studies reporting cost and resource use data in adult patients with IPF or PPF in the UK. Full details of the review methods, including eligibility criteria, search strategies, and quality assessment tools, are provided in Appendix E.[139]

Based on the results of the SLR, and examination of previous relevant appraisals in IPF and PPF[18, 47, 51, 80], the economic model included the following cost components:

- Intervention and comparators' costs and resource use, including drug acquisition and administration costs and liver function monitoring costs and usage
- Health state unit costs and resource use, including disease monitoring and supplementary oxygen costs
- Adverse reaction unit costs and resource use
- Miscellaneous unit costs and resource use, including acute exacerbations and end of life costs

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In line with the NICE reference case[128], the model was built from the perspective of the NHS and PSS; therefore, where possible, HCRU cost inputs were sourced from the NHS Reference Costs 2024/25[140] and PSSRU 2024.[141] Where necessary, costs were inflated to the 2024 cost year using the NHS Cost Inflation Indices published by the PSSRU.[141]

3.5.1 Intervention and comparators' costs and resource use

3.5.1.1 Drug administration and acquisition costs

Drug acquisition unit costs and doses are the same for both IPF and PPF indications (summarised in Table 61), with pirfenidone only relevant to the IPF indication. The list prices were informed by the British National Formulary[142] for nintedanib and by the UK electronic market information tool (eMIT)[143] for pirfenidone (both accessed in November 2025). Information on the treatment dosing schedule was extracted from the product labels.[84, 90, 144, 145] Drug administration costs are assumed to be zero because all relevant treatments have an oral route of administration.

For IPF, a lower per cycle unit cost was applied to pirfenidone in the first cycle to account for the label-recommended dose escalation period upon treatment initiation, with a pirfenidone dose of 267 mg three times daily (801 mg/day) in the first week, 534 mg three times daily (1,602 mg/day) in the second week, and 801 mg three times daily (2,403 mg/day) thereafter. After treatment discontinuation, patients are assumed to receive BSC, which results in no drug acquisition costs for subsequent treatments. The drug acquisition costs per model cycle are summarised in Table 62.

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Table 61: List price unit costs for each treatment included in the model

Treatment	Package size	Strength (mg)	Cost per pack (£)	Daily dose (mg)	Tablets per day
NERA 18 mg	60	18	3,825	36	2
NDB	60	150	2,151	300	2
PFN first week	63	267	14.59	801	3
PFN second week	63	267	14.59	1,602	6
PFN after 2 weeks	90	801	42.69	2,403	3

Key: BNF, British National Formulary; eMIT, electronic market information tool; FVC, forced vital capacity; NDB, nintedanib; NERA, nerandomilast; PFN, pirfenidone; PPF, progressive pulmonary fibrosis; SE, standard error.
Note: A dose intensity of 100% and a discount of 0% were assumed for all included treatments.
Source: NDB cost per pack extracted from BNF[142]; PFN cost per pack extracted from eMIT.[143]

Table 62: Drug acquisition costs per model cycle

Treatment	Drug acquisition cost per cycle (£)
NERA 18 mg	7,531
BSC	0.00
NDB	6,547
PFN first cycle	117.50
PFN after first cycle	121.57

Key: BSC, best supportive care; NDB, nintedanib; NERA, nerandomilast; PFN, pirfenidone.

With PAS discounts, the pack costs are [redacted] for nerandomilast and [redacted] for nintedanib. This translates to costs per model cycle of [redacted] for nerandomilast and [redacted] for nintedanib.

3.5.1.2 Liver function test costs

Current standard of care can be associated with liver damage and routine monitoring of liver function via blood tests is mandated in the pirfenidone marketing authorisation[90] and recommended in the nintedanib NHS guidelines for use.[88, 89] In line with previous economic models, it was assumed that liver function monitoring is routinely performed for patients receiving AF treatments.[123] Therefore, the costs and disutilities (Section 3.4.6) associated with liver function monitoring were accounted for in the model, and were applied exclusively to patients receiving AF treatments (nintedanib and pirfenidone), in both IPF and PPF.

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Following discussions with clinical experts[93], it was noted that the previous approach to costing liver function monitoring – based on just the NHS Reference Costs 2024/25 (£4.35) – appeared to be too low; it did not fully account for the administrative and nursing time required. Hence, a 10-minute nurse appointment cost was also included (£7.50).[140, 141] Clinical feedback suggests that nurse appointment time was typically longer, and so a scenario which considered a 60-minute nurse appointment was also included in the model.

The model assumes that liver function monitoring is conducted once every 3 months (i.e. once per cycle), except during the first cycle, when tests are performed monthly to monitor AF tolerability. This schedule was confirmed through clinical consultation[93], although worth noting that pirfenidone's marketing authorisation stipulates monthly liver function monitoring for the first 6 months.[90]

3.5.2 Health state unit costs and resource use

3.5.2.1 Disease monitoring costs

Resource use items and frequency of use were obtained from FIBRONEER trial data. Costs associated with disease management, monitoring and patient follow-up are included in the economic model, in line with the NICE reference case. Separate resource use was assumed for each of the FVC % predicted states as resource use is expected to differ depending on the status of the disease. The model uses a micro-costing approach using unit cost and per cycle frequency inputs for multiple different resource use components. Hospitalisations due to acute exacerbations (within 90 days of an event) were excluded from health state specific calculations as they were incorporated separately. Rates were calculated as the number of events divided by the total patient months within each FVC % predicted category, where patient months represent the cumulative follow-up time for all patients in that category. Separate rates and proportions were reported for hospitalisations, emergency room visits, and outpatient visits, including the proportion involving intensive care unit (ICU) admission, mechanical ventilation, ambulance use, overnight emergency room stay, and relation to the trial diagnosis. Per cycle frequencies for IPF and PPF are presented in Table 63 and Table 64, respectively.

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The unit costs for each component included in the model were sourced from either the NHS Reference Costs 2024/25[140] or PSSRU 2024[141], as reported in Table 65. The unit cost for the category 'Other visits' was calculated as an average of non-elective inpatient stays (short stays) and outpatient attendances.

The resulting per cycle disease monitoring costs are shown in Table 66. In both IPF and PPF, the HRCU cost is relatively stable across FVC % predicted categories, with a sharp increase only observed for FVC % predicted < 50.[123]

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Table 63: Per cycle frequencies of disease monitoring categories in the IPF population

FVC % pred	Hosp wo ICU	Hosp w ICU	A&E visits	Amb use	GP visits	Spec visits	Nurse visits	Physio visits	OT visits	Other visits
≥ 110	0.07	0.01	0.03	0.01	0.20	0.33	0.01	0.03	0.00	0.03
100–109.9	0.06	0.01	0.05	0.01	0.16	0.25	0.02	0.00	0.00	0.01
90–99.9	0.04	0.01	0.07	0.02	0.12	0.19	0.01	0.01	0.00	0.02
80–89.9	0.06	0.01	0.05	0.02	0.15	0.17	0.01	0.01	0.00	0.03
70–79.9	0.06	0.01	0.05	0.02	0.15	0.17	0.03	0.01	0.00	0.02
60–69.9	0.05	0.01	0.06	0.02	0.12	0.18	0.02	0.00	0.00	0.03
50–59.9	0.08	0.01	0.07	0.03	0.24	0.20	0.06	0.01	0.00	0.02
40–49.9	0.09	0.01	0.10	0.04	0.14	0.22	0.06	0.07	0.00	0.02
30–39.9	0.22	0.01	0.15	0.07	0.11	0.26	0.07	0.00	0.00	0.04

Key: A&E, accident and emergency; Amb, ambulance; FVC % pred, forced vital capacity percent predicted; GP, general practitioner; Hosp, hospitalisation; ICU, intensive care unit; IPF, idiopathic pulmonary fibrosis; OT, occupational therapist; Physio, physiotherapist; Spec, specialist; w, with; wo, without.

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Table 64: Per cycle frequencies of disease monitoring categories in the PPF population

FVC % pred	Hosp wo ICU	Hosp w ICU	A&E visits	Amb use	GP visits	Spec visits	Nurse visits	Physio visits	OT visits	Other visits
≥ 110	0.03	0.01	0.04	0.02	0.25	0.17	0.00	0.03	0.00	0.03
100–109.9	0.11	0.01	0.08	0.07	0.24	0.21	0.00	0.01	0.00	0.03
90–99.9	0.05	0.01	0.03	0.01	0.16	0.30	0.03	0.01	0.00	0.06
80–89.9	0.07	0.01	0.06	0.01	0.13	0.23	0.02	0.00	0.00	0.04
70–79.9	0.08	0.01	0.04	0.01	0.18	0.24	0.03	0.01	0.00	0.02
60–69.9	0.08	0.01	0.07	0.02	0.16	0.24	0.01	0.01	0.00	0.03
50–59.9	0.07	0.01	0.07	0.02	0.15	0.26	0.04	0.01	0.01	0.04
40–49.9	0.13	0.01	0.09	0.04	0.12	0.30	0.05	0.01	0.01	0.02
30–39.9	0.28	0.01	0.11	0.08	0.21	0.52	0.02	0.00	0.00	0.01

Key: A&E, accident and emergency; Amb, ambulance; FVC % pred, forced vital capacity percent predicted; GP, general practitioner; Hosp, hospitalisation; ICU, intensive care unit; OT, occupational therapist; Physio, physiotherapist; PPF, progressive pulmonary fibrosis; Spec, specialist; w, with; wo, without.

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Table 65: Disease monitoring unit costs

Component	Unit cost (£)	Currency code/reference table
Hospitalisations without ICU (per stay)	4,009	NHS Reference Costs 2024/25; Fibrosis or Pneumoconiosis; Per Stay, NEL. Currency Code: DZ25
ICU stay with or without mechanical ventilation (per day)	1,855	NHS Reference Costs 2024/25; Adult Critical Care, 0-1 Organs Supported; Per Day. Currency Codes: XC06Z; XC07Z
A&E visits	333.75	NHS Reference Costs 2024/25; ER overnight stay. Emergency Medicine, Category 1-5 investigation, Category 1-5 treatment; Per Visit. Currency code: VB01Z-VB09Z
Ambulance use	271.98	NHS Reference Costs 2024/25; Ambulance codes 01 - 04
GP visits	45.00	PSSRU 2024, Table 9.4.2; Unit costs for a GP: Per surgery consultation lasting 10 minutes
Specialist visits	206.85	NHS Reference Costs 2024/25; Consultant Led: Respiratory Medicine Service Non-Admitted Face to Face, follow-up. Currency code: 340
Nurse visits	176.45	NHS Reference Costs 2024/25; Specialist Nursing, Asthma and Respiratory Nursing/Liaison, Adult, Face to face - Community Health Services. Respiratory Service. Currency Code: N08AF
Physiotherapist visits	212.91	NHS Reference Costs 2024/25; Physiotherapist, Adult, One to One - Community Health Services. Respiratory Service. Currency code: A08A1
Occupational therapy visits	249.46	NHS Reference Costs 2024/25; Occupational Therapist, Adult, One to One - Community Health Services. Respiratory Service. Currency Code: A06A1
Other visits	511.00	PSSRU 2024, Table 6.1; Average of Non-elective inpatient stays (short stays) and Outpatient attendances

Key: A&E, accident and emergency; GP, general practitioner; ICU, intensive care unit; NEL, non-elective long stay; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.
Source: Unit costs for the categories ‘GP visits’ and ‘Other visits’ were extracted from the PSSRU 2024 Report. All other unit costs were extracted from the NHS National Cost Collection (2024/25).

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Table 66: Per cycle disease monitoring costs

FVC % predicted	IPF cost per cycle (£)	PPF cost per cycle (£)
≥ 110	402.39	233.19
100–109.9	342.63	578.94
90–99.9	239.31	312.22
80–89.9	338.34	377.90
70–79.9	317.18	422.95
60–69.9	299.01	436.07
50–59.9	443.02	426.91
40–49.9	517.29	668.52
30–39.9	1,069	1,316
Key: FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.		

3.5.2.2 Supplementary oxygen costs

The proportion of patients with supplemental oxygen use by FVC % predicted were derived from FIBRONEER. Additionally, a distinction was made between patients who required oxygen therapy before and after experiencing an episode of acute exacerbation, with percentages validated by UK clinicians, who broadly agreed with the inputs.[93] UK clinician feedback indicated that most of the patients who survive an acute exacerbation will require supplemental oxygen therapy for the remainder of their lives.[116] FVC % predicted-specific shares of patients needing oxygen therapy before and after acute exacerbation are detailed in Table 67.

The unit cost of supplemental oxygen therapy was obtained from the NHS Reference Costs 2024/25[140], and adjusted to align with the cycle length within the model. A scenario was also examined using an alternative supplemental oxygen source from a previous appraisal (TA747), included for consistency with earlier assessments.[47] This source uses a cost of £527.57. Costs associated with supplemental oxygen therapy were included in the analysis as FVC % predicted-specific per cycle costs (Table 68).

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Table 67: Share of patients requiring oxygen therapy before and after acute exacerbation for IPF and PPF

	Share of patients on oxygen therapy IPF		Share of patients on oxygen therapy PPF	
FVC % predicted	**Before acute exacerbation**	**After acute exacerbation**	**Before acute exacerbation**	**After acute exacerbation**
≥ 110	[redacted]	[redacted]	[redacted]	[redacted]
100–109.9	[redacted]	[redacted]	[redacted]	[redacted]
90–99.9	[redacted]	[redacted]	[redacted]	[redacted]
80–89.9	[redacted]	[redacted]	[redacted]	[redacted]
70–79.9	[redacted]	[redacted]	[redacted]	[redacted]
60–69.9	[redacted]	[redacted]	[redacted]	[redacted]
50–59.9	[redacted]	[redacted]	[redacted]	[redacted]
40–49.9	[redacted]	[redacted]	[redacted]	[redacted]
30–39.9	[redacted]	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]

Key: DBL, data base lock; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.
Notes: The reported N of patients is based on patient visits. Share of patients on oxygen therapy after acute exacerbation was calculated by applying an adjustment factor of 2.77 for IPF and 2.09 for PPF to the before acute event distribution. The adjustment factor was calculated by dividing the weighted averages of patients needing oxygen after and before acute exacerbation (64.69%/23.34%) and (59.78%/28.65%), respectively.
Source: FIBRONEER-IPF E41932-00 Evidera, PPD 20 June 2025, PPF DBL2 Statistical Analysis.[105]

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Table 68: Per cycle supplemental oxygen therapy costs

	Cost per cycle of supplemental oxygen therapy (IPF)		Cost per cycle of supplemental oxygen therapy (PPF)	
FVC % predicted	**Before acute exacerbation (£)**	**After acute exacerbation (£)**	**Before acute exacerbation (£)**	**After acute exacerbation (£)**
≥ 110	29.65	82.18	0.00	0.00
100–109.9	30.80	85.35	47.90	99.96
90–99.9	28.42	78.75	47.53	99.18
80–89.9	40.78	113.02	45.81	95.58
70–79.9	51.34	142.27	52.13	108.78
60–69.9	75.45	209.09	69.54	145.10
50–59.9	85.64	237.34	91.36	190.63
40–49.9	138.92	246.89	121.98	246.89
30–39.9	192.49	246.89	176.94	246.89

Key: FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.
Source: NHS Reference Costs 2024/25[140]

3.5.3 Adverse reaction unit costs and resource use

As outlined in Section 3.3.6, Grade 3+ AEs are included in the economic model. The costs associated with managing these AEs were sourced from the NHS Reference Costs 2024/25 and are presented in Table 69.[140] The costs are applied as a one-off cost accrued in the first model cycle (assuming that incurred AEs are not long-lasting and mostly happen during the initial treatment period). The total AE cost per treatment arm is presented in Table 70.

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Table 69: Unit costs for adverse events

Adverse event	Unit cost (monthly, £)	Source	Notes
Cardiac events	2,652	NHS Reference Costs 2024/25[140]	Cardiac Arrest; Per Stay; Weighted average of NES and NEL. Currency code: EB05
Pneumonia	8,102		Lobar, Atypical or Viral Pneumonia, with Multiple Interventions; Per Stay, Weighted average of NES and NEL. Currency Code: DZ11K-M
Diarrhoea	6,168		Gastrointestinal Infections with Single Intervention. Currency code FD01C-D
GI disorders (without diarrhoea)	6,415		Gastrointestinal Infections with Single Intervention. Currency code FD01C-D
Photosensitivity reaction	6,415		Skin Disorders with Interventions. Currency code: JD07A-C
Key: GI, gastrointestinal; NEL, non-elective long stay; NES, non-elective short stay; NHS, National Health Service.			

Table 70: Total AE-related cost (£) per treatment arm

Indication	Nerandomilast	Nintedanib	BSC	Pirfenidone
IPF	622.61	637.80	784.93	724.38
PPF	1,080	1,243	1,009	N/A
Key: AE, adverse event; BSC, best supportive care; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.				

3.5.4 Miscellaneous unit costs and resource use

3.5.4.1 Acute exacerbation costs

As described in Section 3.3.4, the risk of acute exacerbations is modelled explicitly for both IPF and PPF patients. To account for costs associated with acute exacerbations, a one-off cost per event of £1,641 is applied from NHS Reference Costs 2024/25 calculated using a weighted average of all acute exacerbation patients with and without hospitalisation (code DZ22).[140]

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3.5.4.2 End of life costs

Patients were assumed to incur a one-off terminal care cost before death. This cost was calculated using data from PSSRU 2024 as the average of hospital decedents (£23,470) and non-hospital decedents (£18,905), then adjusted to reflect a 3-month cycle value.[141] A scenario analysis was undertaken using end of life costs from a recent NICE appraisal (TA1108) [146], which derived costs based on the distribution of patients across home, hospital, and hospice care settings. Unit costs for this scenario were sourced from PSSRU 2024, NHS Reference Costs 2024/25, and assumptions reported in NICE TA531.[140, 141, 147] The end of life costs used in the model are presented in Table 71.

Table 71: End of life costs used in the model

Scenario	Cost per event (£)	SE (£)	Source
Base case	2,570	514	PSSRU 2024 Table 7.2.2[141]
Scenario	5,968	1,194	NICE TA1108[146]
Key: NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; SE, standard error; TA, technology appraisal.			

3.6 Severity

People living with IPF or PPF face a decline not only in their life expectancy but also in their overall quality of life compared with the general population. In the base case analysis, the model estimated the total QALYs expected for patients receiving BSC. These figures were compared with QALY estimates for the general population (derived as per Section 3.4.6), allowing calculation of both the absolute and proportional QALY shortfall.

A summary of the QALY shortfall analysis is presented in Table 72. The expected discounted QALYs for people living with IPF and PPF receiving BSC are detailed in Table 73. These are based on the model results described in Section 3.10. For all treatments in both populations, the absolute QALY shortfalls are all below 12 and the proportional QALY shortfalls are all less than 85%; therefore no multiplier for disease severity is considered appropriate for any of the comparisons.

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Table 72: Summary features of QALY shortfall analysis

Factor	IPF	PPF	Reference to section in submission
Male distribution (%)	76.0	49.8	Section 3.2.1
Starting age (years)	70.4	66.2	
Key: IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis; QALY, quality-adjusted life year.			

Table 73: Summary of QALY shortfall analysis

Comparator	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
BSC; PPF	10.19	3.32	6.87	67.39%	1
BSC; IPF	8.62	3.40	5.23	60.62%	1
Key: BSC, best supportive care; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis; QALY, quality-adjusted life year.					

3.7 Uncertainty

There are several important sources of uncertainty in both the clinical evidence and the economic modelling for this technology. These arise from the limitations in the pivotal trial data, gaps in subsequent treatment information, and challenges in the use of real-world evidence (RWE). Each has been addressed, where possible, through sensitivity and scenario analyses, although residual uncertainty remains.

The FIBRONEER-IPF ‘no AF background therapy’ cohort is small, with only 87 patients and only three observed deaths over the follow-up period in the nerandomilast arm during the follow-up. In the FIBRONEER-ILD ‘no AF background therapy’ cohort, 15 deaths were recorded among 220 patients. As a result, model inputs derived directly from these sub groups – including utilities, AE frequencies, OS and FVC decline) carry a degree of statistical uncertainty. To address this uncertainty, a series of sensitivity analyses were conducted that either varied key parameters or drew on alternative data sources or assumptions where appropriate.

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This approach tests the robustness of the results while acknowledging the limitations inherent in the available sub-group data. Despite their limitations, the FIBRONEER trials remain the primary and most relevant and reliable source of information.

Additionally, the FIBRONEER trials have a limited follow-up period ([redacted] years for FIBRONEER-IPF and [redacted] years for FIBRONEER-ILD), resulting in immature OS data for both the overall study population and the 'no AF background therapy cohort'. Numbers at risk are low, particularly towards the tail of the Kaplan–Meier curves, which increases uncertainty around longer-term survival estimates. Comparator OS data are also immature (1.73 years INPULSIS and 2.32 years INBUILD), compounding the uncertainty in relative treatment effects. In the economic model, this was addressed by testing alternative survival extrapolation methods, including alternative distributions and those incorporating acute exacerbations as predictors. The approach to survival extrapolation was validated by clinical experts (Section 3.3.3).[93, 116]

As noted in Section 2.7, the proportion of patients who initiated subsequent treatment after discontinuing nerandomilast was small.[110, 111] This was due to a combination of the small overall patient numbers, short follow-up periods, and the fact that relatively few patients discontinued treatment during the trials. As such, it was not possible to determine if the observed OS reflects a continued benefit of nerandomilast after discontinuation, or if there would be treatment waning. In the base-case, the treatment effect was assumed to cease after four cycles following discontinuation based on clinical opinion. After this period, efficacy was assumed to be equal to BSC, although it was also noted that there may also be a 'legacy protective effect' of treatment with nerandomilast. It was not possible to quantify this, and as such the true effectiveness of nerandomilast may be underestimated. This structural assumption was tested in scenario analyses.

There is considerable uncertainty surrounding the acute exacerbation results from FIBRONEER. Acute exacerbations are difficult to define consistently (see Section 1.3.1), and the number of observed events was low in both treatment arms in FIBRONEER-IPF (11 events for nerandomilast and 12 events for BSC) and FIBRONEER-ILD (30 events for nerandomilast and 55 events for BSC). These

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factors reduce the statistical power to detect differences between treatment arms across both populations. From a modelling perspective, these limitations create uncertainty in whether acute exacerbations should be included as a predictive factor for mortality or disease progression. In the base-case model, acute exacerbations were not used as a predictor of other outcomes, to avoid introducing additional noise into their modelling. Instead, their impact was explored in scenario analyses using alternative structural approaches where acute exacerbations were included as covariates.

Finally, there is an absence of standardised clinical coding for diagnosis of PPF. In routine practice, a patient's underlying ILD diagnosis code is recorded regardless of whether they subsequently develop PPF phenotype. Over time, a proportion of non-IPF ILD patients progress to PPF; this proportion varies across ILD subtypes. Consequently, accurately identifying patients with PPF—and determining the timing of PPF diagnosis - in routinely collected data remains challenging and is currently not feasible.

Additionally, algorithms using the medical and ICD-10 codes for identification of patients with IPF were shown to be of weak to moderate positive predicted value.[148] These challenges in coding of ILD diagnosis make it difficult to identify comparable patient cohorts and introduce uncertainty when attempting to align RWE with the characteristics of the trial population. Hence, the role of RWE in informing or validating the economic model inputs and results was limited. Scenario analyses were undertaken to explore the impact of alternative inputs; however, these alternative values often originated from the same evidence sources used in previous NICE appraisals, such as TA747, and therefore may not fully capture the uncertainty associated with broader real-world variability.

3.8 Managed access proposal

The company does not intend to submit a managed access proposal for the present technology appraisal.

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3.9 Summary of base case analysis inputs and assumptions

3.9.1 Summary of base case analysis inputs

The base case model parameters are summarised in Table 74.

Table 74: Summary of variables used in the economic model

Variable	Value	SE or N	Within PSA varied by	Reference to section in submission
Settings				
Cycle length (months)	3	–	Not varied	Section 3.2.2
Discount rate – effect	3.5%	–	Not varied	
Discount rate – cost	3.5%	–	Not varied	
Baseline characteristics – IPF				
Age	70.40	0.52	Normal	Section 3.2.1
Proportion of males	76.00%	262	Beta	
Baseline characteristics – PPF				
Age	66.20	0.40	Normal	Section 3.2.1
Proportion of males	49.80%	662	Beta	
Baseline FVC % predicted – IPF				
≥ 110	[redacted]	262	Beta Dirichlet	Section 3.3.2.1
100–109.9	[redacted]			
90–99.9	[redacted]			
80–89.9	[redacted]			
70–79.9	[redacted]			
60–69.9	[redacted]			
50–59.9	[redacted]			
40–49.9	[redacted]			
30–39.9	[redacted]			
Baseline FVC % predicted – PPF				
≥ 110	[redacted]	662	Beta Dirichlet	Section 3.3.2.2
100–109.9	[redacted]			

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Variable	Value	SE or N	Within PSA varied by	Reference to section in submission
90–99.9	[redacted]			
80–89.9	[redacted]			
70–79.9	[redacted]			
60–69.9	[redacted]			
50–59.9	[redacted]			
40–49.9	[redacted]			
30–39.9	[redacted]			
Efficacy				
Risk of mortality	Gamma joint model	–	–	Section 3.3.3
Change in FVC	Poisson regression model	–	–	Section 3.3.2
Risk of acute exacerbation (probability per cycle)	Exponential joint model	–	–	Section 3.3.4
Treatment discontinuation	Exponential separate models	–	–	Section 3.3.5
Treatment cost				
Acquisition cost: Nerandomilast 18 mg x 60	List price: £3,825 PAS price: [redacted]	Section 3.5.1.1		
Acquisition cost: Nintedanib 150 mg x 60	List price: £2,151 PAS price: [redacted]			
Acquisition cost: Pirfenidone 267 mg x 63	List price: £14.59			
Acquisition cost: Pirfenidone 801 mg x 84	List price: £42.69			
Resource use				
LFM cost	£4.35	£0.87	Gamma	Section 3.5.1.2
LFM nurse cost	£7.50	£1.50	Gamma	
Hosp without ICU cost	£4,008.97	£801.79	Gamma	Section 3.5.2.1
Hosp with ICU cost	£1,854.90	£370.98	Gamma	

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Variable	Value	SE or N	Within PSA varied by	Reference to section in submission
A&E visit cost	£333.75	£66.75	Gamma	
Ambulance use cost	£271.98	£54.40	Gamma	
GP visit cost	£45.00	£9.00	Gamma	
Specialist visit cost	£206.85	£41.37	Gamma	
Nurse visit cost	£176.45	£35.29	Gamma	
Physio visit cost	£212.91	£42.58	Gamma	
OT visit cost	£249.46	£49.89	Gamma	
Other visit cost	£511.00	£102.20	Gamma	
HCRU frequency – IPF	Table 63	–	Gamma	
HCRU frequency – PPF	Table 64	–	Gamma	
SupOx cost	£246.89	£49.38	Gamma	Section 3.5.2.2
SupOx frequency	Table 67	–	Beta	
Acute exacerbation	£1,641.46	£328.29	Gamma	Section 3.5.4.1
End of life	£2,569.25	£513.48	Gamma	Section 3.5.4.2
Adverse event				
Cardiac events cost	£2,651.93	£530.39	Gamma	Section 3.5.3
Pneumonia cost	£8,101.82	£1,620.36	Gamma	
Diarrhoea cost	£6,168.19	£1,233.64	Gamma	
GI disorders cost (without diarrhoea)	£6,414.80	£1,282.96	Gamma	
Photosensitivity reaction cost	£6,414.80	£1,282.96	Gamma	
AE frequencies	Table 47	–	Beta	Section 3.3.6
Utilities				
Health state utilities – IPF	Table 57	–	VarCovar	Section 3.4.1.1
Health state utilities – PPF	Table 59	–	VarCovar	Section 3.4.1.2

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Variable	Value	SE or N	Within PSA varied by	Reference to section in submission
Acute exacerbation disutility – IPF	[redacted]	–	VarCovar	Section 3.4.1.1
Acute exacerbation disutility – PPF	[redacted]	–	VarCovar	Section 3.4.1.2
LFM testing disutility	0.0230	0.0046	Beta	Section 3.4.5
AE disutilities	Table 55	–	Gamma	Section 3.4.4

Key: A&E, accident and emergency; AE, adverse event; FVC, forced vital capacity; GI, gastrointestinal; GP, general practitioner; HCRU, healthcare resource use; Hosp, hospitalisation; ICU, intensive care unit; IPF, idiopathic pulmonary fibrosis; LFM, liver function monitoring; N, number; OT, occupational therapist; PAS, patient access scheme; Physio, physiotherapist; PPF, progressive pulmonary fibrosis; PSA, probabilistic sensitivity analysis; SE, standard error; SupOx, supplemental oxygen; VarCovar, variance–covariance matrix.

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3.9.2 Assumptions

Key assumptions of the economic analysis are summarised in Table 75. The approach to modelling has been designed to make the best use of the available data to inform the decision problem. In the absence of data, assumptions are designed to minimise potential bias in the analysis. These have been reviewed and validated by clinical experts where appropriate.[93, 116]

Table 75: Key assumptions in the economic analysis

Category	Assumption	Justification
Model structure and settings	Lifetime time horizon	Aligned with prior economic models reviewed for IPF and PPF.[18, 47, 51, 80] Based on the starting age in FIBRONEER, the time horizon is 30 years for IPF and 34 years for PPF. It is assumed no patients survive beyond a mean age of 100 years. At this time point within the model, ~100% patients are dead
	A cycle length of 3 months is used	Aligned with prior economic models reviewed for IPF and PPF.[18, 47, 51, 80] Clinical experts also noted that a 3-monthly cycle is granular enough to capture the average trajectory of IPF and PPF patients in terms of FVC % predicted decline, risk of AcEx and OS[116]
	UK NHS and PSS perspective	In line with NICE reference case[128]
	The model health states capture the elements of the disease and care pathway that are important for patient health outcomes and NHS England costs	The Markov cohort state transition approach was selected given it was previously utilised across published economic models and previous HTAs in IPF and PPF.[18, 47, 51, 80] Furthermore, the selected model structure captures the key FIBRONEER trials' outcomes, with FVC % Pred decline directly related to the primary endpoint and time to first AcEx and time to death being part of the key secondary endpoint
Clinical effectiveness	Pirfenidone efficacy assumed equal to nintedanib (IPF only)	This assumption was verified with clinicians and is consistent with prior NICE appraisals[80, 93]
	Efficacy and safety of BSC were assumed to be represented by the control (PBO) arm of the FIBRONEER trials	Patients were allowed to use certain background therapies in case of acute exacerbations or disease decline after 6 months on therapy, which is similar to current BSC

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Category	Assumption	Justification
	For mortality and acute exacerbations, the relative effectiveness of nintedanib was obtained from IPD meta-regression	IPD meta-regression represents the 'gold standard' approach to ITC, allowing for adjustment of differences in patient characteristics
	Decline in FVC % predicted is modelled using a Poisson regression framework	This approach avoids the bias seen when applying logistic regression models to the FIBRONEER trials. Poisson regression measures declines relative to baseline, reducing noise and penalising treatments less when early improvements are observed
	Each progression event is defined as a ≥ 10% drop in FVC % predicted from baseline	Anchoring decline thresholds to baseline ensures that only clinically meaningful deterioration from the patient's starting status is counted, consistent with trial definitions and reducing misclassification from short-term fluctuations
	A constant rate of FVC % predicted decline is assumed across the time horizon, with separate values applied for patients above and below the median, where the median is 80 for IPF and 70 for PPF.	This simplifies modelling, increases statistical power and aligns with the Poisson framework and observed event rates in the trial. Similar constant-rate event modelling has precedence in NICE TAs where short-term noise could bias results
	Exponential distributions (constant hazard) are used for extrapolation in both IPF and PPF for AcEx rates	Exponential models provided the best statistical fit and were judged clinically plausible by clinical experts in IPF/PPF.[80, 93] This assumption is consistent with prior Markov models in IPF/PPF
	Exponential distribution (constant hazard) are used for extrapolation in IPF and PPF for treatment discontinuation	This approach provided an acceptable fit, plausible long-term extrapolations as validated by clinical experts in IPF/PPF, and consistency with observed trial follow-up.[80, 93]
	Stopping rule applied to all active treatment for a drop in FVC decline greater than 10%	Formal stopping rules exist for nintedanib in IPF, and clinical experts note that this is the approach applied in practice for pirfenidone in IPF and nintedanib in PPF.[80, 93]
	Treatment effect waning	Following discontinuation of active treatment, treatment efficacy wanes to that of BSC. This waning is delayed until 2.75 years after treatment initiation in the IPF population and 3.0 years in the PPF population.

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Category	Assumption	Justification
	Only severe (Grade 3+) AEs with a frequency ≥ 5% in the nerandomilast arms of the FIBRONEER trials, or Grade 3+ AEs included in previous NICE TAs for IPF/PPF, are modelled	This threshold ensures only clinically significant and economically relevant AEs are included, in line with prior NICE appraisal methods for IPF/PPF[18, 47, 51, 80]
	AE costs are applied as a one-off cost upon treatment initiation ("frontloading" approach)	Serious AEs typically occur early in treatment; frontloading reflects this clinical reality and is consistent with previous NICE submissions for IPF/PPF[18, 47, 51, 80]
Cost and resource use inputs	No treatment cost was assumed for the BSC arm	This aligns with previous appraisals where analysis on concomitant medications showed a small difference between trial arms[18, 47, 51, 80]
	Patients receiving AF treatment receive an LFM once a month for the first 3 months, and once every 3 months thereafter	AFs require monthly liver tests for the first 3 months, followed by regular checks as clinically indicated – many centres recommend quarterly thereafter in the UK, as supported by clinical experts.[84, 90, 93]
	End of life costs applied as a one-off cost in the year at which patients die	Patients will accrue end of life care costs before they die and therefore, they are applied within the year of death
Utilities	A health-state utility approach is used, assigning utility values by FVC % predicted health state	Patients with higher FVC % predicted are expected to have better HRQL than those with lower FVC, consistent with clinical evidence and NICE reference case methodology[93, 116, 128]
	AE-related disutilities are applied for patients experiencing Grade 3+ AEs; values vary by AE type and are applied for one model cycle	Consistent with previous NICE appraisals to reflect short-term HRQL impact[18, 47, 51, 80]

Key: AcEx, acute exacerbation; AE, adverse event; AF, antifibrotic; BSC, best supportive care; FVC, forced vital capacity; HRQL, health-related quality of life; HTA, health technology assessment; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; ITC, indirect treatment comparison; LFM, liver function monitoring; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PBO, placebo; PPF, progressive pulmonary fibrosis; PSS, Personal Social Services; SmPC, Summary of Product Characteristics; TA, technology appraisal; TTD, time to discontinuation.

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3.10 Base case results

3.10.1 Base case incremental cost-effectiveness analysis results

3.10.1.1 IPF

At PAS price for both nerandomilast and nintedanib, the total costs in each arm are [redacted], £12,609, [redacted] and £13,625 for nerandomilast, BSC, nintedanib and pirfenidone, respectively. The total QALYs were 4.54, 3.40, 3.61 and 3.61 for nerandomilast, BSC, nintedanib and pirfenidone, respectively. The estimated incremental cost-effectiveness ratio (ICER) for nerandomilast versus BSC [redacted] per QALY, nerandomilast versus nintedanib is [redacted] per QALY, and nerandomilast versus pirfenidone is [redacted] per QALY. The fully incremental deterministic results of nerandomilast versus the comparators are presented in Table 76 using PAS prices. Pairwise results of nerandomilast versus BSC, nintedanib and pirfenidone using PAS prices, are presented in Table 77, Table 78 and Table 79, respectively.

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Table 76: Fully incremental base case results – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	12,609	4.46	3.40	-	-	-	-
Pirfenidone	13,625	4.74	3.61	1,016	0.28	0.21	4,831
Nintedanib	[redacted]	4.74	3.61	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	5.96	4.54	[redacted]	1.22	0.93	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 77: Base case pairwise results nerandomilast versus BSC – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Nerandomilast	[redacted]	5.96	4.54	-	-	-	-	-	-
BSC	12,609	4.46	3.40	[redacted]	1.50	1.14	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

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Table 78: Base case pairwise results nerandomilast versus nintedanib – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Nerandomilast	[redacted]	5.96	4.54	-	-	-	-	-	-
Nintedanib	[redacted]	4.74	3.61	[redacted]	1.22	0.93	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.									

Table 79: Base case pairwise results nerandomilast versus pirfenidone – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Nerandomilast	[redacted]	5.96	4.54	-	-	-	-	-	-
Pirfenidone	13,625	4.74	3.61	[redacted]	1.22	0.93	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.									

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3.10.1.2 PPF

At PAS price for both nerandomilast and nintedanib, the total costs were [redacted], £17,458 and [redacted] for nerandomilast, BSC and nintedanib, respectively. The total QALYs were 4.12, 3.32 and 3.77 for nerandomilast, BSC and nintedanib, respectively. The estimated ICER for nerandomilast versus BSC is [redacted] per QALY, and nerandomilast versus nintedanib is [redacted] per QALY. The fully incremental deterministic results of nerandomilast versus the comparators are presented in Table 80 using PAS prices. Pairwise results of nerandomilast versus BSC, nintedanib and pirfenidone using PAS prices, are presented in Table 81 and Table 82, respectively.

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Table 80: Fully incremental base case results – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	17,458	4.65	3.32	-	-	-	-
Nintedanib	[redacted]	5.26	3.77	[redacted]	0.62	0.45	[redacted]
Nerandomilast	[redacted]	5.74	4.12	[redacted]	0.47	0.35	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 81: Base case pairwise results nerandomilast versus BSC – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Nerandomilast	[redacted]	5.74	4.12	-	-	-	-	-	-
BSC	17,458	4.65	3.32	[redacted]	1.09	0.80	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 82: Base case pairwise results nerandomilast versus nintedanib – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Nerandomilast	[redacted]	5.74	4.12	-	-	-	-	-	-
Nintedanib	[redacted]	5.26	3.77	[redacted]	0.47	0.35	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

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3.10.1.3 Weighted average ICER

Weighted average results combining the IPF and PPF population results are presented in Table 83, Table 84 and Table 85, incorporating confidential discounts for nerandomilast and nintedanib. The weighting is based on the reported prevalence of IPF in TA864 (10 per 100,000) and of PPF in TA747 (1.5 per 100,000), as reported in Section 1.3.1.2.[47, 80] The weighted average ICER for nerandomilast was [redacted] per QALY gained versus BSC, and [redacted] per QALY gained versus nintedanib.

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Table 83: Fully incremental base case results – PAS prices; IPF+PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	13,242	4.48	3.39	-	-	-	-
Nintedanib	[redacted]	4.81	3.63	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	5.93	4.48	[redacted]	1.45	1.10	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 84: Base case pairwise results nerandomilast versus BSC – PAS prices; IPF+PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Nerandomilast	[redacted]	5.93	4.48	-	-	-	-	-	-
BSC	13,242	4.48	3.39	[redacted]	1.45	1.10	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 85: Base case pairwise results nerandomilast versus nintedanib – PAS prices; IPF+PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Nerandomilast	[redacted]	5.93	4.48	-	-	-	-	-	-
Nintedanib	[redacted]	4.81	3.63	[redacted]	1.12	0.85	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

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3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

To explore uncertainty around the key model variables in the base case, a probabilistic sensitivity analysis (PSA) was performed (1,000 iterations). Whenever available, the standard error of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on parameter variability, a standard error of 10% of the mean was assumed. More detail on the parameters included in the PSA, along with their assumed distributions and standard error and confidence limits can be found in Section 3.9.1.

3.11.1.1 IPF

Pairwise results of the PSA using PAS prices are presented in Table 86, Table 87 and Table 88 for nerandomilast versus BSC, nintedanib, and pirfenidone, respectively. The cost-effectiveness plane of incremental costs and incremental QALYs from the PSA with PAS prices is presented in Figure 47 with a willingness-to-pay threshold of £20,000 per QALY gained, and Figure 48 with a willingness-to-pay threshold of £30,000 per QALY gained. Figure 49 presents the cost-effectiveness acceptability curve (CEAC), showing the likelihood of each comparator being the most cost-effective at different willingness-to-pay thresholds.

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Table 86: Mean PSA pairwise results for nerandomilast versus BSC – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Nerandomilast	[redacted]	5.94	4.51	-	-	-
BSC	12,924	4.53	3.44	[redacted]	1.06	[redacted]
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.						

Table 87: Mean PSA pairwise results for nerandomilast versus nintedanib – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Nerandomilast	[redacted]	5.94	4.51	-	-	-
Nintedanib	[redacted]	4.69	3.56	[redacted]	0.95	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.						

Table 88: Mean PSA pairwise results for nerandomilast versus pirfenidone – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Nerandomilast	[redacted]	5.94	4.51	-	-	-
Pirfenidone	13,629	4.69	3.56	[redacted]	0.95	[redacted]
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.						

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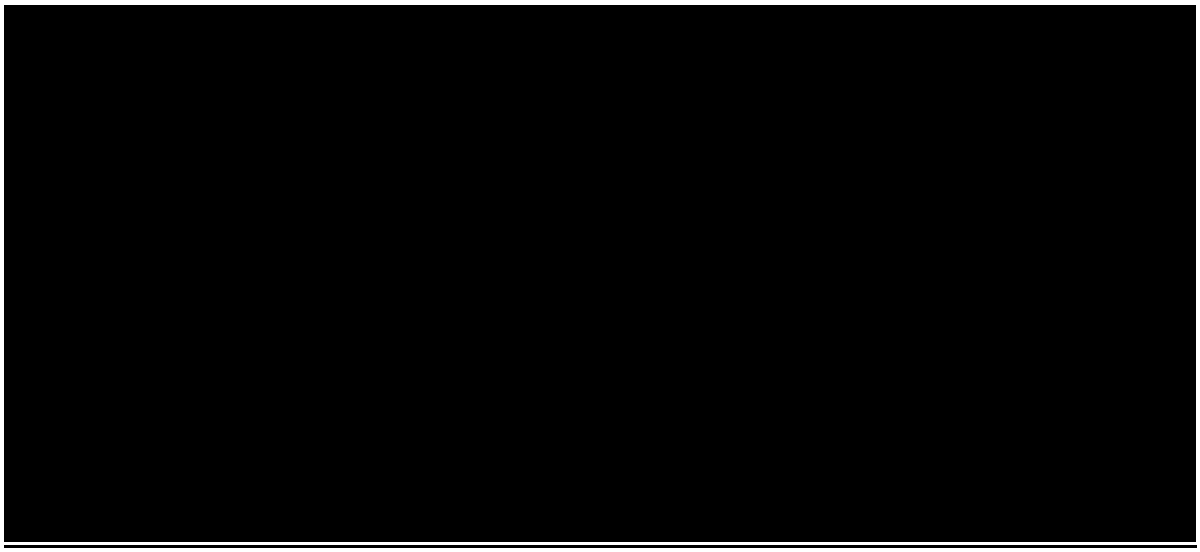
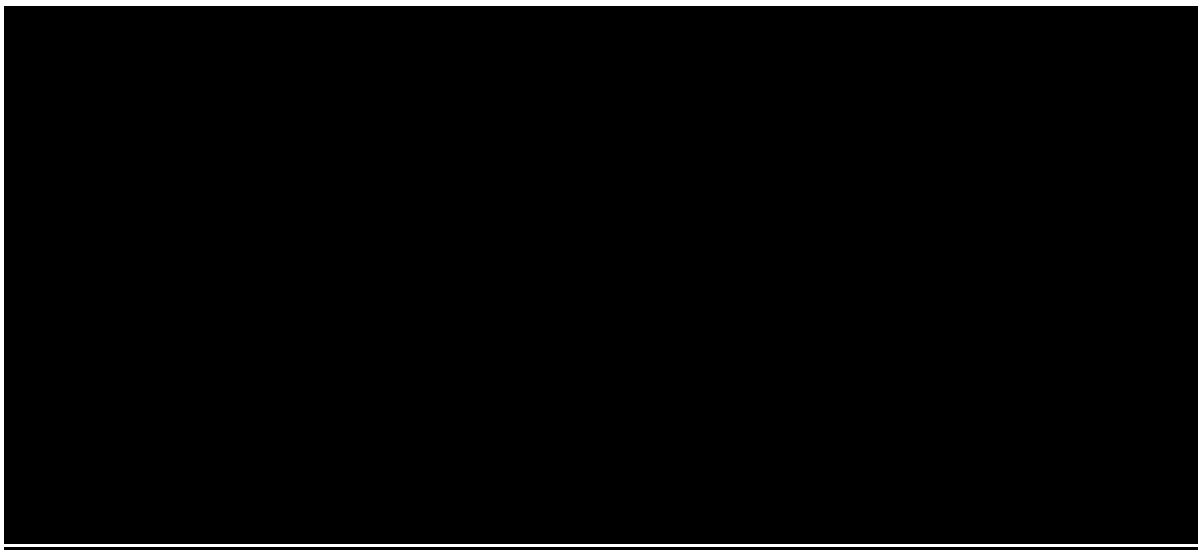
Figure 47: Cost-effectiveness plane for nerandomilast at a WTP of £20,000 – PAS prices; IPF



Key: BSC, best supportive care; NDB, nintedanib; NERA, nerandomilast; PFN, pirfenidone; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 48: Cost-effectiveness plane for nerandomilast at a WTP of £30,000 – PAS prices; IPF



Key: BSC, best supportive care; NDB, nintedanib; NERA, nerandomilast; PFN, pirfenidone; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.

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Figure 49: Cost-effectiveness acceptability curve – PAS prices; IPF



Key: BSC, best supportive care; NDB, nintedanib; NERA, nerandomilast; PFN, pirfenidone

3.11.1.2 PPF

Pairwise results of the PSA using PAS prices are presented in Table 89 and Table 90 for nerandomilast versus BSC and nintedanib, respectively. The cost-effectiveness plane of incremental costs and incremental QALYs from the PSA with PAS prices is presented in Figure 50 with a willingness-to-pay threshold of £20,000 per QALY gained, and Figure 51 with a willingness-to-pay threshold of £30,000. Figure 52 presents the CEAC, showing the likelihood of each comparator being the most cost-effective at different willingness-to-pay thresholds.

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Table 89: Mean PSA pairwise results for nerandomilast versus BSC – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Nerandomilast	[redacted]	5.73	4.09	-	-	-
BSC	17,697	4.69	3.32	[redacted]	0.76	[redacted]
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.						

Table 90: Mean PSA pairwise results for nerandomilast versus nintedanib – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Nerandomilast	[redacted]	5.73	4.09	-	-	-
Nintedanib	[redacted]	5.25	3.74	[redacted]	0.35	[redacted]
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.						

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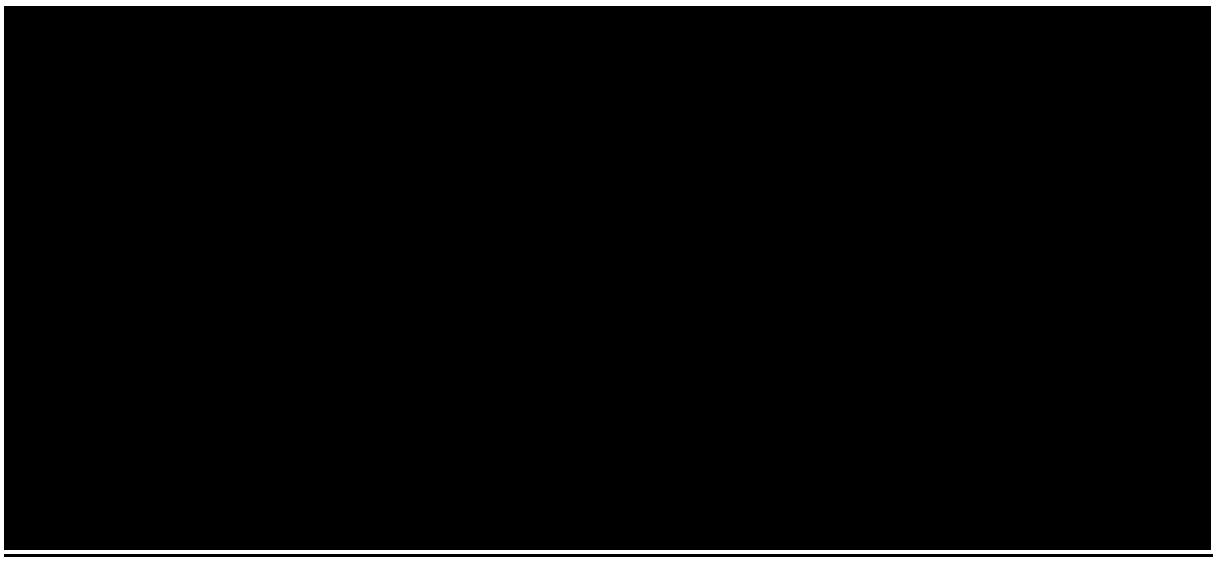
Figure 50: Cost-effectiveness plane for nerandomilast at a WTP of £20,000 – PAS prices; PPF



Key: BSC, best supportive care; NDB, nintedanib; NERA, nerandomilast; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 51: Cost-effectiveness plane for nerandomilast at a WTP of £30,000 – PAS prices; PPF



Key: BSC, best supportive care; NDB, nintedanib; NERA, nerandomilast; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.

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Figure 52: Cost-effectiveness acceptability curve – PAS prices; PPF



Key: BSC, best supportive care; NDB, nintedanib; NERA, nerandomilast

3.11.2 Deterministic sensitivity analysis

The sensitivity of the model results and drivers of cost-effectiveness were explored with a one-way sensitivity analysis (OWSA), where tests were performed around the 95% CI values of all model parameters.

3.11.2.1 IPF

Figure 53, Figure 54 and Figure 55 present the results of the OWSA in the form of tornado diagram at PAS prices. Each figure shows the 10 parameters with the most influence on the ICER (£/QALY) for each pairwise comparison with nerandomilast. Treatment-based mortality parameters for nerandomilast, mortality HRs for nerandomilast versus nintedanib, and the treatment waning switch are among the most influential for each comparator.

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Figure 53: OWSA tornado diagram for nerandomilast versus BSC – PAS prices, IPF



Key: AE, adverse event; AF, antifibrotic; BID, twice a day; BSC, best supportive care; FVC, forced vital capacity; HS, health state; ICER, incremental cost-effectiveness ratio; IPF, idiopathic pulmonary fibrosis; NERA, nerandomilast; OWSA, one-way sensitivity analysis; PAS, patient access scheme; QALY, quality-adjusted life year; RU, resource use; TP, transition probability; TTD, time to treatment discontinuation.

Figure 54: OWSA tornado diagram for nerandomilast versus nintedanib – PAS prices, IPF



Key: AE, adverse event; AF, antifibrotic; BID, twice a day; FVC, forced vital capacity; HR, hazard ratio; HS, health state; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib; NERA, nerandomilast; OWSA, one-way sensitivity analysis; PAS, patient access scheme; QALY, quality-adjusted life year; RU, resource use; TP, transition probability; TTD, time to treatment discontinuation.

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Figure 55: OWSA tornado diagram for nerandomilast versus pirfenidone – PAS prices, IPF



Key: AF, antifibrotic; BID, twice a day; FVC, forced vital capacity; HR, hazard ratio; HS, health state; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib; NERA, nerandomilast; OWSA, one-way sensitivity analysis; PAS, patient access scheme; QALY, quality-adjusted life year; RU, resource use; TP, transition probability.

3.11.2.2 PPF

Figure 56 and Figure 57 present the results of the OWSA in the form of tornado diagram at PAS prices. Each figure shows the 10 parameters with the most influence on the ICER (£/QALY) for each pairwise comparison with nerandomilast. Treatment-based mortality parameters for nerandomilast, treatment waning switch point, and discontinuation probability per cycle are among the most influential for each comparator.

Figure 56: OWSA tornado diagram for nerandomilast versus BSC – PAS prices, PPF



Key: AE, adverse event; AF, antifibrotic; BID, twice a day; BSC, best supportive care; FVC, forced vital capacity; HS, health state; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; NERA, nerandomilast; OWSA, one-way sensitivity analysis; PAS, patient access scheme; PPF, progressive pulmonary fibrosis; QALY, quality-adjusted life year; RU, resource use; TP, transition probability; TTD, time to treatment discontinuation.

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Figure 57: OWSA tornado diagram for nerandomilast versus nintedanib – PAS prices, PPF



Key: AF, antifibrotic; BID, twice a day; FVC, forced vital capacity; HS, health state; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; NDB, nintedanib; NERA, nerandomilast; OWSA, one-way sensitivity analysis; PAS, patient access scheme; PPF, progressive pulmonary fibrosis; QALY, quality-adjusted life year; RU, resource use; TP, transition probability; TTD, time to treatment discontinuation.

3.11.3 Scenario analysis

To further explore uncertainty within the model, an extensive list of scenarios was tested. These scenarios were listed throughout Section 3.

3.11.3.1 IPF

The results of the scenario analyses (reported in Table 91 using PAS prices) show that the onset of treatment waning and modelling of mortality have the greatest impact on the base case ICER. Overall, the results of the scenario analysis indicate that the base case results are robust, as the changes implemented as part of these scenarios had little impact on the overall results.

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Table 91: Scenario analysis results for IPF – PAS prices

Scenario	Category	Base case value	Scenario value	Rationale	ICER vs BSC (£/QALY)	ICER vs NDB (£/QALY)	ICER vs PFN (£/QALY)
-	Base case				[redacted]	[redacted]	[redacted]
1	NDB treatment effect source (all efficacy endpoints)	IPD meta-regression*	Using INPULSIS data	Explore a wide range of potential treatment effect sources given that nintedanib was not a direct comparator in the trial	[redacted]	[redacted]	[redacted]
2	Health state transitions	Equal to NERA	NDB = IPD meta-regression	Estimate the impact of health state transitions differing between treatments	[redacted]	[redacted]	[redacted]
3			PFN = NMA		[redacted]	[redacted]	[redacted]
4			NDB = IPD meta-regression; PFN = NMA		[redacted]	[redacted]	[redacted]
5		Not dependent on AcEx	Increased risk following AcEx		[redacted]	[redacted]	[redacted]
6	Mortality	Gamma	Weibull	Exploring alternative models that were noted as plausible by clinicians for robustness	[redacted]	[redacted]	[redacted]
7			Log-logistic		[redacted]	[redacted]	[redacted]
8		FIBRONEER trial data for NERA	NERA ITC results	Using more mature data for nerandomilast	[redacted]	[redacted]	[redacted]
9	AcEx	Vary by treatment	Equal to NERA for all treatments	Based on clinical validation	[redacted]	[redacted]	[redacted]

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Scenario	Category	Base case value	Scenario value	Rationale	ICER vs BSC (£/QALY)	ICER vs NDB (£/QALY)	ICER vs PFN (£/QALY)
10		Constant	Vary by health state		[redacted]	[redacted]	[redacted]
11	TTD	Stopping rule for all treatments	Stopping rule for NERA only	Impact of formal stopping rule for nerandomilast and comparators	[redacted]	[redacted]	[redacted]
12		Waning of [redacted] cycles	Waning of [redacted] cycles	Alignment with FIBRONEER-IPF follow-up	[redacted]	[redacted]	[redacted]
13		Constant discontinuation rate	Parametric-based discontinuation rate	Clinical validation, discontinuation rate may not be constant	[redacted]	[redacted]	[redacted]
14	Health state utilities	Pooled FIBRONEER-IPF and INPULSIS	Literature (Rinciog 2017)[123]	Impact of using previously accepted utility values in NICE TA747.[47, 123]	[redacted]	[redacted]	[redacted]
15	Disutility of acute exacerbation	Pooled FIBRONEER-IPF and INPULSIS	INPULSIS	Based on clinical validation: pooled trial-based utilities after acute exacerbation higher than clinicians expected	[redacted]	[redacted]	[redacted]
16	Costs	SupOx costs: NHS Ref 24/25	SupOx costs: Rinciog 2017	Alignment with earlier TAs in this area	[redacted]	[redacted]	[redacted]
17		EoL costs: PSSRU	EoL costs: TA1108	Exploring the impact of using a greater cost of EoL	[redacted]	[redacted]	[redacted]

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Scenario	Category	Base case value	Scenario value	Rationale	ICER vs BSC (£/QALY)	ICER vs NDB (£/QALY)	ICER vs PFN (£/QALY)
18		Nurse time LFM: 10 min	Nurse time LFM: 60 min	Clinical feedback notes that 10 minutes too short	[redacted]	[redacted]	[redacted]

Key: AcEx, acute exacerbation; EoL, end of life; FVC, forced vital capacity; ICER, incremental cost-effectiveness ratio; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; ITC, indirect treatment comparison; LFM, liver function monitoring; NDB, nintedanib; NERA, nerandomilast; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PFN, pirfenidone; PSSRU, Personal Social Services Research Unit; SupOx, supplemental oxygen; TA, technology appraisal; TTD, time to treatment discontinuation.
Notes: *for change in FVC over time the base case value for nintedanib is equal to nerandomilast.

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3.11.3.2 PPF

The results of the scenario analyses (reported in Table 92 using PAS prices) show that the onset of treatment waning and modelling of mortality have the greatest impact on the base case ICER. Overall, the results of the scenario analysis indicate that the base case results are robust, as the changes implemented as part of these scenarios had little impact on the overall results.

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Table 92**: Scenario analysis results for PPF – PAS prices**

Scenario	Category	Base case value	Scenario value	Rationale	ICER vs BSC (£/QALY)	ICER vs NDB (£/QALY)
-	Base case				[redacted]	[redacted]
1	NDB treatment effect source (all efficacy endpoints)	IPD meta-regression*	Using INPULSIS data	Explore a wide range of potential treatment effect sources given that nintedanib was not a direct comparator in the trial	[redacted]	[redacted]
2	Health state transitions	Equal to NERA	NDB = IPD meta-regression	Estimate the impact of health state transitions differing between treatments	[redacted]	[redacted]
3		Not dependent on AcEx	Increased risk following AcEx		[redacted]	[redacted]
4	Mortality	Gamma	Weibull	Exploring alternative models that were noted as plausible by clinicians for robustness	[redacted]	[redacted]
5			Log-normal		[redacted]	[redacted]
6		FIBRONEER trial data for NERA	NERA ITC results	Using more mature data for nerandomilast	[redacted]	[redacted]
7	AcEx	Vary by treatment	Equal to NERA for all treatments	Based on clinical validation	[redacted]	[redacted]
8		Constant	Vary by health state		[redacted]	[redacted]
9	TTD	Stopping rule for all treatments	Stopping rule for NERA only	Impact of formal stopping rule for nerandomilast and comparators	[redacted]	[redacted]
10		Waning of [redacted] cycles	Waning of [redacted] cycles	Alignment with FIBRONEER-ILD follow-up	[redacted]	[redacted]

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Scenario	Category	Base case value	Scenario value	Rationale	ICER vs BSC (£/QALY)	ICER vs NDB (£/QALY)
11		Constant discontinuation rate	Parametric-based discontinuation rate	Clinical validation, discontinuation rate may not be constant	[redacted]	[redacted]
12	Health state utilities	Pooled FIBRONEER-ILD and INBUILD	Literature (TA747)[123]	Impact of using previously accepted utility values in NICE TA747.[47, 123]	[redacted]	[redacted]
13	Disutility of acute exacerbation	Pooled FIBRONEER-ILD and INBUILD	INBUILD	Based on clinical validation: pooled trial-based utilities after acute exacerbation higher than clinicians expected	[redacted]	[redacted]
14	Costs	SupOx costs: NHS Ref 24/25	SupOx costs: Rinciog 2017	Alignment with earlier TAs in this area	[redacted]	[redacted]
15		EoL costs: PSSRU	EoL costs: TA1108	Exploring the impact of using a greater cost of EoL	[redacted]	[redacted]
16		Nurse time LFM: 10 min	Nurse time LFM: 60 min	Clinical feedback notes that 10 minutes too short	[redacted]	[redacted]

Key: AcEx, acute exacerbation; EoL, end of life; FVC, forced vital capacity; ICER, incremental cost-effectiveness ratio; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; ITC, indirect treatment comparison; LFM, liver function monitoring; NDB, nintedanib; NERA, nerandomilast; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PFN, pirfenidone; PSSRU, Personal Social Services Research Unit; SupOx, supplemental oxygen; TA, technology appraisal; TTD, time to treatment discontinuation.
Notes: *for change in FVC over time the base case value for nintedanib is equal to nerandomilast.

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3.12 Subgroup analysis

No subgroup analyses were conducted for this evaluation. This decision was based on the absence of evidence from the FIBRONEER trials indicating any statistically or clinically meaningful differences in outcomes across the predefined subgroups.

3.13 Benefits not captured in the QALY calculation

A pragmatic approach was taken to the economic model. As a result, some of the advantages of nerandomilast were omitted to enhance the simplicity and transparency of the model. Hence, the cost-effectiveness of nerandomilast is likely to be underestimated. One important omission is the short-term improvement in FVC % predicted observed with nerandomilast. This represents a meaningful physiological gain for patients, yet it couldn't be captured within the standard statistical analyses used within the current economic model. In addition, potential treatment effects whereby disease progression remains slowed or stability is extended, are protected only until 2.75 or 3 years after treatment initiation in the model, and any additional protective legacy following discontinuation is not reflected in the model. Both effects could deliver incremental survival and quality of life benefits beyond those quantified in the base case.

The model also does not capture the major operational (capacity) advantages associated with nerandomilast's safety and monitoring profile. No requirement for liver function monitoring, no need for dose titration (as with pirfenidone), fewer AE monitoring visits and visits for pausing/restarting therapy, and a lower need for oxygen supplementation could free up substantial health care professional time. These efficiencies directly support the NHS Long Term Plan's commitments to optimise outpatient care, reduce unnecessary hospital visits, and improve workforce capacity in overstretched services such as respiratory medicine. In addition to the quantified impact on the ICER, clinicians regard these as significant operational advantages of nerandomilast, who stated "*The greatest threat to our service right now is the inability to get bloods done… this removes that barrier*", "*Our nurses and pharmacists are spending hours literally handwriting blood forms to post to other parts of the region*" and "*Just the initiation is going to be easier… that is a huge pro*".[81]

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The impact on carers and on work productivity are similarly excluded. Evidence from the PFT survey and a Delphi panel suggest the burden of pulmonary fibrosis extends to carers/spouses/loved ones, as described Section 1.3.3.1.1). These societal aspects, including caregiver burden and lost productivity for both patients and carers, are not factored into the QALY estimates. As noted in Section 1.3.3.2, a significant proportion of patients with PPF report having to modify or leave employment. Preserving lung function could help maintain economic activity for longer, with benefits extending beyond the patient.

Another notable consideration is that, for both IPF and PPF, nerandomilast is the first drug in many years (since nintedanib) to successfully complete a Phase 3 trial. This represents a major milestone for patients and clinicians, offering renewed hope and signalling that further innovation is possible. Access to this treatment has the potential not only to improve outcomes directly but also to stimulate ongoing research and investment in new therapies for fibrotic lung disease.

Finally, for a subset of patients, lung transplantation remains a potential treatment option. Stabilising disease could extend the period during which patients remain eligible, preserving this life-saving pathway for longer. This benefit is not reflected in the economic model.

In summary, there are several elements of value for nerandomilast that are not currently quantified in the economic modelling. These include early improvements in FVC coupled with potential protective legacy effects, substantial healthcare capacity gains through reduced monitoring and AE management, reduced carer burden, preserved patient productivity, extended transplant eligibility, and the broader innovation signal of the first successful Phase 3 therapy in years. Many of these benefits align closely with the NHS Long Term Plan’s priorities, supporting prevention of deterioration, greater system efficiency, workforce optimisation, and improved outcomes in chronic respiratory disease. Recognition of these omitted benefits is essential for a complete assessment of value.

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3.14 Validation

A range of validation activities were undertaken to ensure the robustness, accuracy and clinical relevance of the model.

The model structure, key model inputs, and underlying assumptions were reviewed by leading UK clinical experts to confirm that the representation of disease progression and treatment pathways reflect the clinical course of the disease and aligns with current NHS practice. This analysis went through three independent rounds of clinical review with different experts: UK clinicians who provided input on the global model structure, UK clinicians who provided input on the adapted UK model, and a thorough review with clinicians to discuss the positioning of nerandomilast in the patient pathway.[81, 93, 116]

Independent quality assurance was conducted by a senior modeller within the developer's organisation who had no involvement in the model's construction, providing an impartial review. In addition, the manufacturer undertook internal validation by systematically varying various parameters and assumptions in the model and investigating the impact on outputs. Further assurance of methodological soundness and transparency was provided through an external technical validation of the model by a health economics specialist using the TECH-VER checklist.[149]

Finally, as described in Section 1.1.1.1, a series of sensitivity analyses were performed to test the stability of the results under plausible alternative parameter values and assumptions, identifying the factors with the greatest potential impact on cost-effectiveness outcomes.

Together, these activities provide a high degree of confidence in the validity and reliability of the model and its suitability for informing this cost-effectiveness assessment.

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3.15 Interpretation and conclusions of economic evidence

This appraisal has been conducted in accordance with NICE methods guidance and established precedent from previous TAs for comparable interventions, and extensively validated.[18, 47, 51, 80, 128] Our approach has been intentionally conservative, ensuring that the economic case presented is both robust and appropriately cautious in its assumptions.

The clinical effectiveness inputs are drawn from robust Phase III RCTs, FIBRONEER-IPF and FIBRONEER-ILD, which compared nerandomilast with BSC (placebo arm). The trials provide high quality evidence for relative treatment effects, with ongoing follow up for OS in FIBRONEER-ON. While the FIBRONEER trials provide no head-to-head evidence against current AF therapy, access to IPD for both nerandomilast and nintedanib pivotal trials is a unique advantage of this appraisal and allows robust ITC to fill this evidence gap.-quality evidence for relative treatment effects, with ongoing follow-up for OS

Consistent with previous appraisals, the economic model is structured around the change in lung function. While providing robust modelling of disease progression in terms of lung function decline, the model analyses are also conservative as they do not account for the initial short-term improvement in FVC % predicted observed in the FIBRONEER trials, as a conservative, pragmatic choice not to overcomplicate the model.

While the current evidence base provides data up to 100 weeks and OS data remain immature, this limitation has been addressed through conservative modelling choices (Gamma curves), extensive validation with clinicians and extensive sensitivity analyses. Furthermore, a robust structured expert elicitation is being conducted to validate long-term OS extrapolations.

In addition, TTD has not been modelled as a cost only input; instead, discontinuation impacts both costs and efficacy. This approach produces more realistic cost effectiveness estimates. The approach to TTD extrapolation and treatment waning cut-off have also been explored in sensitivity analyses, which demonstrates that

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results are robust to the chosen survival model.-only input; instead, -effectiveness estimates

3.15.1 Conclusions

For IPF, the deterministic base case yields an ICER of [redacted] per QALY gained compared with BSC, [redacted] per QALY gained compared with nintedanib, and [redacted] per QALY gained compared with pirfenidone. Results are similar for the probabilistic results, with ICERs of [redacted], [redacted], and [redacted] per QALY gained, for nerandomilast versus BSC, nintedanib and pirfenidone, respectively.

For PPF, the deterministic base case yields an ICER of [redacted] per QALY gained compared with BSC, and [redacted] per QALY gained compared with nintedanib. Results are similar the probabilistic results, with ICERs of [redacted] and [redacted] per QALY gained, for nerandomilast versus BSC and nintedanib, respectively.

When weighted averages across both IPF and PPF are considered, the deterministic base case yields an ICER of [redacted] per QALY gained compared with BSC, and [redacted] per QALY gained compared with nintedanib.

Across both populations, scenario and one-way sensitivity analyses suggest that the approach to modelling mortality, treatment waning, and treatment discontinuation are key drivers of cost-effectiveness results. Overall, cost-effectiveness results were robust to alternative approaches and assumptions.

In conclusion, despite uncertainties including immature OS data for nerandomilast and uncertainties in post-discontinuation treatment efficacy, the totality of evidence demonstrates that nerandomilast provides meaningful clinical benefit in an area of high unmet need, addressing a gap in current care provision and aligning with NHS priorities to improve patient outcomes in IPF and PPF.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis [ID6446]

Company addendum

April 2026

File name	Version	Contains confidential information	Date
ID6446 Nerandomilast company addendum	**1.0**	**Yes**	**29 April 2026**

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Purpose of this addendum

The company has identified an error in the economic model for nerandomilast in idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF) that affects the PPF results submitted in the company submission (CS), the budget impact analysis (BIA), and responses to clarification questions (CQs). The hazard ratio (HR) for mortality from the individual patient data (IPD) meta-regression indirect treatment comparison (ITC) for nerandomilast versus nintedanib in PPF has been corrected to [redacted] (95% confidence interval [CI]: [redacted]), as reported in Table 19 of the company submission and in the IPD meta-regression report shared with the Evidence Assessment Group (EAG) during the clarification stage.

Please note, the HRs for TTD have also been corrected in the model for both IPF (corrected to [redacted] [95% CI: [redacted]]) and PPF (corrected to [redacted] [95% CI: [redacted]]) to align with the IPD meta-regression results presented in Section 2.11.3 of the submission document. The TTD HRs are not used in calculations so this correction had no impact on the cost-effectiveness results. Please also note, all HRs from the IPD meta-regression have been updated to three decimal points to align with the results available in the IPD meta-regression report shared with the EAG during the clarification stage.

This addendum document presents corresponding updated results for PPF in the following documents and sections:

- Company submission:
  - Summary of cost-effectiveness of nerandomilast vs nintedanib in PPF (summary box at the beginning of Section 3)
  - Short-term and long-term overall survival (OS) extrapolations for nintedanib (Figure 42 in the CS) and landmark survival estimates for nintedanib (Table 42 in the CS), in Section 3.3.3
  - Base case results for PPF (Section 3.10.1.2)
  - Weighted average ICER (Section 3.10.1.3)
  - Exploring uncertainty for PPF (Sections 3.11.1.2, 3.11.2.2 and 3.11.3.2)
  - Interpretation and conclusions of economic evidence (Section 3.15)

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- Budget impact analysis:
  - Costs per patient per year for nintedanib in PPF (Table 13)
  - Expected budget impact (PAS prices) in PPF (Table 17)

- Clarification questions responses
  - Response to question B6: Tables 13 and 15
  - Response to question B7: Table 18
  - Response to question B9: response text and Table 25

Updates to company submission

Objective:

- To examine the cost-effectiveness of nerandomilast versus current treatment options for patients with IPF or PPF

Model overview:

- A de novo cohort-level Markov model was developed, with health states based on FVC % predicted in 10 percentage point intervals
- Analyses were conducted over a lifetime horizon from the English National Health Service (NHS) and Personal Social Services (PSS) perspective
- In IPF, the comparators were BSC, nintedanib and pirfenidone
- In PPF, the comparators were BSC and nintedanib

Key model inputs and assumptions:

- Clinical data (FVC changes, OS, risk of acute exacerbation and TTD) used in this economic analysis were based on the results from the pivotal FIBRONEER trials for nerandomilast and BSC, and INBUILD and INPULSIS trials for nintedanib
  - Health state transitions (change in FVC % predicted) were determined using a Poisson regression model

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  - Extrapolations of OS, acute exacerbations and TTD were conducted in accordance with NICE technical support document (TSD) 14[1] to obtain long-term estimates to support the model
  - The base case OS extrapolations follow a gamma distribution, based on statistical and visual fit, and clinical plausibility of extrapolations[2, 3]
  - The base case applies a constant risk of acute exacerbation and treatment discontinuation per cycle, differentiated by treatment
  - The base case applies treatment waning to all efficacy outputs and assumes a stopping rule for all active treatments if the patient experiences a drop of FVC % predicted greater than 10%
- Health state utility values were informed by pooled EQ-5D-5L data collected in the FIBRONEER-IPF and INPULSIS trials (IPF) and FIBRONEER-ILD and INBUILD trials (PPF), mapped to the third-line (3L) value set using the mapping function developed by the NICE Decision Support Unit[4]
- Costs and HCRU captured in the analysis included drug acquisition and administration costs, liver function monitoring costs, monitoring costs, AE costs, acute exacerbation costs and end of life costs
  - Resource use frequencies were obtained from the FIBRONEER trials
  - The model included Grade 3+ AEs

Results:

- In the base case analysis in IPF, nerandomilast was associated with an ICER of [redacted] per QALY gained versus BSC, [redacted] per QALY gained versus nintedanib and [redacted] per QALY gained versus pirfenidone
- In the base case analysis in PPF, nerandomilast was associated with an ICER of [redacted] per QALY gained versus BSC and [redacted] per QALY gained versus nintedanib
- Results for both populations were most sensitive to mortality parameters, the length of the treatment waning effect, and treatment discontinuation probability
- The weighted average ICER for nerandomilast (assuming 87% of pulmonary fibrosis cases are IPF and 13% are PPF (Section 1.3.1.2)) was [redacted] per QALY gained versus BSC, and [redacted] per QALY gained versus nintedanib

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3.3 Clinical parameters and variables

3.3.3 Risk of mortality

3.3.3.1 IPF

3.3.3.2 PPF

3.3.3.2.1 Summary of FIBRONEER-ILD survival data

Follow-up periods for the FIBRONEER-ILD trial were [redacted] years for nerandomilast and [redacted] years for placebo. A summary of survival data from FIBRONEER-ILD is detailed in Table 38. OS data are shown in Kaplan–Meier graphs for nerandomilast, placebo and nintedanib in Figure 39, based on FIBRONEER-ILD and INBUILD data.

Table 38: Summary of FIBRONEER-ILD survival data

	Nerandomilast	**Placebo**
N	220	222
Number of events	[redacted]	[redacted]
Follow-up (years)	[redacted]	[redacted]
RMST (years)	[redacted]	[redacted]
Key: N, number; RMST, restricted mean survival time.		

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Figure 39: Kaplan–Meier for overall survival based on FIBRONEER-ILD and INBUILD data



Key: KM, Kaplan–Meier; NDB, nintedanib; nera, nerandomilast.

3.3.3.2.2 Proportional hazards assessment

The appropriateness of the PH assumption was assessed using Schoenfeld residuals and log-cumulative hazard plots (see Appendix M). As with IPF, whilst there was potential evidence for a violation of the PH assumption, this was considered likely to be an artefact of the small number of mortality events in FIBRONEER, rather than a true departure from proportionality. Hence, consistent with the IPF analyses, joint survival models were estimated to ensure that consistent treatment effects were modelled.

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3.3.3.2.3 Visual and statistical assessment of fit

Table 39 summarises the goodness of fit for the parametric models to the observed data as assessed using AIC and BIC statistics. The joint parametric models and observed OS Kaplan–Meier data from the FIBRONEER-ILD and INBUILD trials are presented in Figure 40, Figure 41 and Figure 42. Landmark survival estimates for each treatment are presented in Table 40, Table 41 and Table 42.

The assessment of statistical and visual fit concluded that:

- Apart from the exponential and log-normal, all the distributions demonstrated a comparable visual and statistical fit during the trial period; however, there was a considerable uncertainty in the long-term extrapolations
- The exponential model provided a poor fit to the placebo and nintedanib arms, under-estimating survival for the majority of follow-up. The log-normal notably over-estimated survival for nerandomilast at the start of follow-up, followed by a notable under-estimation. These two distributions also had the worst fit based on AIC and BIC
- The Gompertz model had the lowest AIC and BIC values. All models apart from exponential, log-normal and generalised gamma had AIC and BIC values which were very similar to the Gompertz

Table 39: Goodness of fit statistics for mortality in PPF

Distribution	AIC	BIC
Exponential (PH)	[redacted]	[redacted]
Weibull (PH)	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PH, proportional hazards; PPF, progressive pulmonary fibrosis.
Note: Bold text represents the model with the best statistical fit.

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Figure 40: Short-term and long-term OS extrapolations for nerandomilast



Key: KM, Kaplan–Meier; OS, overall survival.

Table 40: Landmark survival estimates for nerandomilast

Distribution	Years				
	1	2	5	10	20
Weibull					
Exponential					
Gamma					
Log-logistic					
Log-normal					
Gompertz					
Note: The landmark survival estimates do not incorporate the treatment waning assumption					

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Figure 41: Short-term and long-term OS extrapolations for placebo



Key: KM, Kaplan–Meier; OS, overall survival.

Table 41: Landmark survival estimates for BSC

Distribution	Years				
	1	2	5	10	20
Weibull					
Exponential					
Gamma					
Log-logistic					
Log-normal					
Gompertz					

Key: BSC, best supportive care.
Note: The landmark survival estimates do not incorporate the treatment waning assumption

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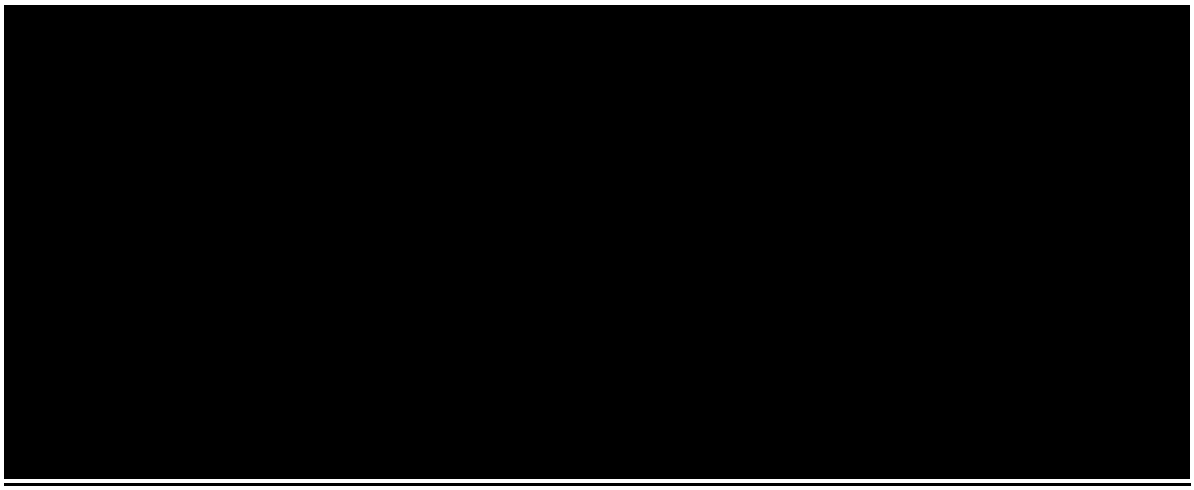
Figure 42: Short-term and long-term OS extrapolations for nintedanib [updated]



Key: KM, Kaplan–Meier; OS, overall survival.

Table 42: Landmark survival estimates for nintedanib [updated]

Distribution	Years				
	1	2	5	10	20
Weibull					
Exponential					
Gamma					
Log-logistic					
Log-normal					
Gompertz					
Note: The landmark survival estimates do not incorporate the treatment waning assumption					

3.3.3.2.4 Clinical expert opinion

As with IPF, expert clinical input was sought regarding the plausibility of the extrapolations from all the survival models. Feedback from clinical experts differed regarding the most appropriate fits for PPF. Respiratory specialists suggested that either the gamma or Weibull models were plausible (for all treatments), whereas rheumatologists preferred the more optimistic exponential and log-normal curves (again, for all treatments).[2] Rheumatologists reflected that the discrepancy may be linked to the type of patients they typically manage, mainly those with comorbid

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rheumatoid arthritis, who often experience a milder disease course and longer survival.[2] The Gompertz model was noted by all UK clinicians as being too pessimistic.[2] In separate validation interviews, respiratory specialists also noted that gamma and Weibull distributions provided the most plausible projections.[3]

3.3.3.2.5 Conclusion

After considering both statistical performance and clinical validation, the gamma distribution was chosen as the preferred option for the base case analysis. While the Gompertz delivered the lowest AIC and BIC scores, clinicians across the UK agreed that it produced overly pessimistic survival projections and was unsuitable for most treatment arms. Feedback from respiratory specialists supported the gamma or Weibull models as the most plausible models, whilst feedback from rheumatologists suggested that the exponential or log-normal models were the most plausible. Of these, the gamma was selected as it lies within 5 points of the best fitting model and is closer aligned to the rheumatologists' opinion. To explore the impact of alternative plausible curves noted by the rheumatologists, Weibull and log-normal models were incorporated into scenario analyses.

Similar to IPF, the model applies a relative treatment effect of nerandomilast versus nintedanib based on a HR calculated in the IPD meta-regression analysis, making best use of the available IPD for this comparison.

3.10 Base case results [updated]

3.10.1 Base case incremental cost-effectiveness analysis results

3.10.1.1 IPF

3.10.1.2 PPF

At PAS price for both nerandomilast and nintedanib, the total costs were [redacted], £17,458 and [redacted] for nerandomilast, BSC and nintedanib, respectively. The total QALYs were 4.12, 3.32 and 3.65 for nerandomilast, BSC and nintedanib, respectively. The estimated ICER for nerandomilast versus BSC is [redacted] per QALY, and nerandomilast versus nintedanib is [redacted] per QALY. The fully incremental deterministic results of nerandomilast versus the comparators are

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presented in Table 80 using PAS prices. Pairwise results of nerandomilast versus BSC, nintedanib and pirfenidone using PAS prices, are presented in Table 81 and Table 82, respectively.

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Table 80: Fully incremental base case results – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	17,458	4.65	3.32	-	-	-	-
Nintedanib	[redacted]	5.09	3.65	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	5.74	4.12	[redacted]	1.09	0.80	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 81: Base case pairwise results nerandomilast versus BSC – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Nerandomilast	[redacted]	5.74	4.12	-	-	-	-	-	-
BSC	17,458	4.65	3.32	[redacted]	1.09	0.80	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 82: Base case pairwise results nerandomilast versus nintedanib – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Nerandomilast	[redacted]	5.74	4.12	-	-	-	-	-	-
Nintedanib	[redacted]	5.09	3.65	[redacted]	0.65	0.47	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

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3.10.1.3 Weighted average ICER

Weighted average results combining the IPF and PPF population results are presented in Table 83, Table 84 and Table 85, incorporating confidential discounts for nerandomilast and nintedanib. The weighting is based on the reported prevalence of IPF in TA864 (10 per 100,000) and of PPF in TA747 (1.5 per 100,000), as reported in Section 1.3.1.2.[5, 6] The weighted average ICER for nerandomilast was [redacted] per QALY gained versus BSC, and [redacted] per QALY gained versus nintedanib.

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Table 83: Fully incremental base case results – PAS prices; IPF+PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	13,242	4.48	3.39	-	-	-	-
Nintedanib	[redacted]	4.79	3.61	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	5.93	4.48	[redacted]	1.45	1.10	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 84: Base case pairwise results nerandomilast versus BSC – PAS prices; IPF+PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Nerandomilast	[redacted]	5.93	4.48	-	-	-	-	-	-
BSC	13,242	4.48	3.39	[redacted]	1.45	1.10	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 85: Base case pairwise results nerandomilast versus nintedanib – PAS prices; IPF+PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Nerandomilast	[redacted]	5.93	4.48	-	-	-	-	-	-
Nintedanib	[redacted]	4.79	3.61	[redacted]	1.15	0.87	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

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3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

3.11.1.1 IPF

3.11.1.2 PPF

Pairwise results of the PSA using PAS prices are presented in Table 89 and Table 90 for nerandomilast versus BSC and nintedanib, respectively. The cost-effectiveness plane of incremental costs and incremental QALYs from the PSA with PAS prices is presented in Figure 50 with a willingness-to-pay threshold of £20,000 per QALY gained, and Figure 51 with a willingness-to-pay threshold of £30,000. Figure 52 presents the CEAC, showing the likelihood of each comparator being the most cost-effective at different willingness-to-pay thresholds.

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Table 89: Mean PSA pairwise results for nerandomilast versus BSC – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Nerandomilast	[redacted]	5.73	4.09	-	-	-
BSC	17,697	4.69	3.32	[redacted]	0.76	[redacted]
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.						

Table 90: Mean PSA pairwise results for nerandomilast versus nintedanib – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Nerandomilast	[redacted]	5.73	4.09	-	-	-
Nintedanib	[redacted]	5.08	3.62	[redacted]	0.47	[redacted]
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.						

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Figure 50: Cost-effectiveness plane for nerandomilast at a WTP of £20,000 – PAS prices; PPF



Key: BSC, best supportive care; NDB, nintedanib; NERA, nerandomilast; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 51: Cost-effectiveness plane for nerandomilast at a WTP of £30,000 – PAS prices; PPF



Key: BSC, best supportive care; NDB, nintedanib; NERA, nerandomilast; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.

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Figure 52: Cost-effectiveness acceptability curve – PAS prices; PPF



Key: BSC, best supportive care; NDB, nintedanib; NERA, nerandomilast

3.11.2 Deterministic sensitivity analysis

The sensitivity of the model results and drivers of cost-effectiveness were explored with a one-way sensitivity analysis (OWSA), where tests were performed around the 95% CI values of all model parameters.

3.11.2.1 IPF

3.11.2.2 PPF

Figure 56 and Figure 57 present the results of the OWSA in the form of tornado diagram at PAS prices. Each figure shows the 10 parameters with the most influence on the ICER (£/QALY) for each pairwise comparison with nerandomilast. Treatment-based mortality parameters for nerandomilast, treatment waning switch point, and discontinuation probability per cycle are among the most influential for each comparator.

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Figure 56: OWSA tornado diagram for nerandomilast versus BSC – PAS prices, PPF



Key: AE, adverse event; AF, antifibrotic; BID, twice a day; BSC, best supportive care; FVC, forced vital capacity; HS, health state; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; NERA, nerandomilast; OWSA, one-way sensitivity analysis; PAS, patient access scheme; PPF, progressive pulmonary fibrosis; QALY, quality-adjusted life year; RU, resource use; TP, transition probability; TTD, time to treatment discontinuation.

Figure 57: OWSA tornado diagram for nerandomilast versus nintedanib – PAS prices, PPF



Key: AF, antifibrotic; BID, twice a day; FVC, forced vital capacity; HS, health state; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; NDB, nintedanib; NERA, nerandomilast; OWSA, one-way sensitivity analysis; PAS, patient access scheme; PPF, progressive pulmonary fibrosis; QALY, quality-adjusted life year; RU, resource use; TP, transition probability; TTD, time to treatment discontinuation.

3.11.3 Scenario analysis

3.11.3.1 IPF

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3.11.3.2 PPF

The results of the scenario analyses (reported in Table 92 using PAS prices) show that the onset of treatment waning and modelling of mortality have the greatest impact on the base case ICER. Overall, the results of the scenario analysis indicate that the base case results are robust, as the changes implemented as part of these scenarios had little impact on the overall results.

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Table 92**: Scenario analysis results for PPF – PAS prices**

Scenario	Category	Base case value	Scenario value	Rationale	ICER vs BSC (£/QALY)	ICER vs NDB (£/QALY)
-	Base case				[redacted]	[redacted]
1	NDB treatment effect source (all efficacy endpoints)	IPD meta-regression*	Using INPULSIS data	Explore a wide range of potential treatment effect sources given that nintedanib was not a direct comparator in the trial	[redacted]	[redacted]
2	Health state transitions	Equal to NERA	NDB = IPD meta-regression	Estimate the impact of health state transitions differing between treatments	[redacted]	[redacted]
3		Not dependent on AcEx	Increased risk following AcEx		[redacted]	[redacted]
4	Mortality	Gamma	Weibull	Exploring alternative models that were noted as plausible by clinicians for robustness	[redacted]	[redacted]
5			Log-normal		[redacted]	[redacted]
6		FIBRONEER trial data for NERA	NERA ITC results	Using more mature data for nerandomilast	[redacted]	[redacted]
7	AcEx	Vary by treatment	Equal to NERA for all treatments	Based on clinical validation	[redacted]	[redacted]
8		Constant	Vary by health state		[redacted]	[redacted]
9	TTD	Stopping rule for all treatments	Stopping rule for NERA only	Impact of formal stopping rule for nerandomilast and comparators	[redacted]	[redacted]
10		Waning of [redacted] cycles	Waning of [redacted] cycles	Alignment with FIBRONEER-ILD follow-up	[redacted]	[redacted]

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Scenario	Category	Base case value	Scenario value	Rationale	ICER vs BSC (£/QALY)	ICER vs NDB (£/QALY)
11		Constant discontinuation rate	Parametric-based discontinuation rate	Clinical validation, discontinuation rate may not be constant	[redacted]	[redacted]
12	Health state utilities	Pooled FIBRONEER-ILD and INBUILD	Literature (TA747)[7]	Impact of using previously accepted utility values in NICE TA747.[5, 7]	[redacted]	[redacted]
13	Disutility of acute exacerbation	Pooled FIBRONEER-ILD and INBUILD	INBUILD	Based on clinical validation: pooled trial-based utilities after acute exacerbation higher than clinicians expected	[redacted]	[redacted]
14	Costs	SupOx costs: NHS Ref 24/25	SupOx costs: Rinciog 2017	Alignment with earlier TAs in this area	[redacted]	[redacted]
15		EoL costs: PSSRU	EoL costs: TA1108	Exploring the impact of using a greater cost of EoL	[redacted]	[redacted]
16		Nurse time LFM: 10 min	Nurse time LFM: 60 min	Clinical feedback notes that 10 minutes too short	[redacted]	[redacted]

Key: AcEx, acute exacerbation; EoL, end of life; FVC, forced vital capacity; ICER, incremental cost-effectiveness ratio; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; ITC, indirect treatment comparison; LFM, liver function monitoring; NDB, nintedanib; NERA, nerandomilast; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PFN, pirfenidone; PSSRU, Personal Social Services Research Unit; SupOx, supplemental oxygen; TA, technology appraisal; TTD, time to treatment discontinuation.
Notes: *for change in FVC over time the base case value for nintedanib is equal to nerandomilast.

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3.15 Interpretation and conclusions of economic evidence

3.15.1 Conclusions

For IPF, the deterministic base case yields an ICER of [redacted] per QALY gained compared with BSC, [redacted] per QALY gained compared with nintedanib, and [redacted] per QALY gained compared with pirfenidone. Results are similar for the probabilistic results, with ICERs of [redacted], [redacted], and [redacted] per QALY gained, for nerandomilast versus BSC, nintedanib and pirfenidone, respectively.

For PPF, the deterministic base case yields an ICER of [redacted] per QALY gained compared with BSC, and [redacted] per QALY gained compared with nintedanib. Results are similar the probabilistic results, with ICERs of [redacted] and [redacted] per QALY gained, for nerandomilast versus BSC and nintedanib, respectively.

When weighted averages across both IPF and PPF are considered, the deterministic base case yields an ICER of [redacted] per QALY gained compared with BSC, and [redacted] per QALY gained compared with nintedanib.

Across both populations, scenario and one-way sensitivity analyses suggest that the approach to modelling mortality, treatment waning, and treatment discontinuation are key drivers of cost-effectiveness results. Overall, cost-effectiveness results were robust to alternative approaches and assumptions.

In conclusion, despite uncertainties including immature OS data for nerandomilast and uncertainties in post-discontinuation treatment efficacy, the totality of evidence demonstrates that nerandomilast provides meaningful clinical benefit in an area of high unmet need, addressing a gap in current care provision and aligning with NHS priorities to improve patient outcomes in IPF and PPF.

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Updates to budget impact analysis

Resources

The frequency and cost of ongoing disease management and monitoring for patients with each FVC % predicted health state are equal across all modelled treatment arms. The most recent NHS reference costs were used to calculate these costs, and most frequencies were obtained from the FIBRONEER trials.[8-10] Further details can be found in Section 3.5.2 of the company submission.

Grade 3+ adverse event incidence and costs (sourced from NHS reference costs) are outlined in Section 3.5.3 of the company submission.[8] The treatment cost of individual adverse events is the same across treatment arms. Incidence data are derived from FIBRONEER for nerandomilast and BSC; INBUILD and INPULSIS for nintedanib; and CAPACITY for pirfenidone.[7, 9-12]

Drug acquisition costs, dosage, treatment schedule and doses received for all modelled comparators are detailed in Section 3.5.1 of the company submission. Drug costs for nintedanib and pirfenidone were sourced from British National Formulary (BNF) and electronic market information tool (eMIT).[13, 14] Patients on AF therapies also incur costs of frequent liver function monitoring as per the relevant prescribing information.[15, 16]

Per patient costs in each year following diagnosis for each comparator are detailed in Table 7–Table 10 for IPF and Table 11–Table 13 for PPF.

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Table 7: Costs per patient per year – nerandomilast; IPF

	Treatment year				
	1	**2**	**3**	**4**	**5**
Acquisition costs (PAS price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment monitoring costs (LFM)	£0	£0	£0	£0	£0
Disease monitoring costs	£1,324	£1,321	£1,300	£1,190	£1,040
Supplemental oxygen therapy costs	£225	£264	£295	£299	£283
Acute exacerbation costs	£137	£152	£147	£141	£119
Adverse event costs*	£628	£0	£0	£0	£0
End-of-life costs	£48	£93	£145	£340	£330
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: IPF, idiopathic pulmonary fibrosis; LFM, liver function monitoring; PAS, patient access scheme.
Note: *Adverse event costs are front-loaded in the first year to align with the approach taken in the cost-effectiveness model

Table 8: Costs per patient per year – BSC; IPF

	Treatment year				
	1	**2**	**3**	**4**	**5**
Acquisition costs	£0	£0	£0	£0	£0
Treatment monitoring costs (LFM)	£0	£0	£0	£0	£0
Disease monitoring costs	£1,295	£1,179	£1,026	£873	£732
Supplemental oxygen therapy costs	£223	£244	£243	£229	£207
Acute exacerbation costs	£153	£154	£129	£104	£83
Adverse event costs*	£781	£0	£0	£0	£0
End-of-life costs	£183	£348	£363	£330	£282
Total	£2,636	£1,925	£1,761	£1,537	£1,304

Key: BSC, best supportive care; IPF, idiopathic pulmonary fibrosis; LFM, liver function monitoring; PAS, patient access scheme.
Note: *Adverse event costs are front-loaded in the first year to align with the approach taken in the

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	Treatment year				
	1	2	3	4	5
cost-effectiveness model					

Table 9: Costs per patient per year – nintedanib; IPF

	Treatment year				
	1	2	3	4	5
Acquisition costs (PAS price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment monitoring costs (LFM)	£65	£22	£12	£6	£3
Disease monitoring costs	£1,303	£1,212	£1,077	£922	£772
Supplemental oxygen therapy costs	£216	£229	£226	£216	£199
Acute exacerbation costs	£91	£95	£86	£105	£86
Adverse event costs*	£644	£0	£0	£0	£0
End-of-life costs	£134	£284	£332	£351	£305
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: IPF, idiopathic pulmonary fibrosis; LFM, liver function monitoring; PAS, patient access scheme.
Note: *Adverse event costs are front-loaded in the first year to align with the approach taken in the cost-effectiveness model

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Table 10: Costs per patient per year – pirfenidone; IPF

	Treatment year				
	1	**2**	**3**	**4**	**5**
Acquisition costs	£408	£223	£116	£59	£29
Treatment monitoring costs (LFM)	£65	£22	£12	£6	£3
Disease monitoring costs	£1,303	£1,212	£1,077	£922	£772
Supplemental oxygen therapy costs	£216	£229	£226	£216	£199
Acute exacerbation costs	£91	£95	£86	£105	£86
Adverse event costs*	£725	£0	£0	£0	£0
End-of-life costs	£134	£284	£332	£351	£305
Total	£2,943	£2,066	£1,850	£1,658	£1,395

Key: IPF, idiopathic pulmonary fibrosis; LFM, liver function monitoring; PAS, patient access scheme.
Note: *Adverse event costs are front-loaded in the first year to align with the approach taken in the cost-effectiveness model

Table 11: Costs per patient per year – nerandomilast; PPF

	Treatment year				
	1	**2**	**3**	**4**	**5**
Acquisition costs (PAS price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment monitoring costs (LFM)	£0	£0	£0	£0	£0
Disease monitoring costs	£1,781	£1,788	£1,762	£1,657	£1,479
Supplemental oxygen therapy costs	£283	£301	£311	£307	£287
Acute exacerbation costs	£83	£89	£83	£118	£107
Adverse event costs*	£1,074	£0	£0	£0	£0
End-of-life costs	£83	£156	£178	£325	£321
Total (PAS price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: LFM, liver function monitoring; PAS, patient access scheme; PPF, progressive pulmonary fibrosis.
Note: *Adverse event costs are front-loaded in the first year to align with the approach taken in the cost-effectiveness model

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Table 12: Costs per patient per year – BSC; PPF

	Treatment year				
	1	**2**	**3**	**4**	**5**
Acquisition costs	£0	£0	£0	£0	£0
Treatment monitoring costs (LFM)	£0	£0	£0	£0	£0
Disease monitoring costs	£1,755	£1,661	£1,513	£1,348	£1,182
Supplemental oxygen therapy costs	£286	£299	£291	£271	£245
Acute exacerbation costs	£154	£155	£130	£107	£87
Adverse event costs*	£1,002	£0	£0	£0	£0
End-of-life costs	£204	£340	£342	£308	£265
Total	£3,401	£2,455	£2,275	£2,034	£1,779

Key: BSC, best supportive care; LFM, liver function monitoring; PPF, progressive pulmonary fibrosis.
Note: *Adverse event costs are front-loaded in the first year to align with the approach taken in the cost-effectiveness model

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Table 13: Costs per patient per year – nintedanib; PPF

	Treatment year				
	1	**2**	**3**	**4**	**5**
Acquisition costs (PAS price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment monitoring costs (LFM)	£64	£21	£10	£5	£3
Disease monitoring costs	£1,760	£1,697	£1,585	£1,435	£1,264
Supplemental oxygen therapy costs	£281	£291	£286	£273	£251
Acute exacerbation costs	£99	£103	£91	£110	£96
Adverse event costs*	£1,222	£0	£0	£0	£0
End-of-life costs	£141	£256	£279	£327	£296
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: LFM, liver function monitoring; PAS, patient access scheme; PPF, progressive pulmonary fibrosis.
Note: *Adverse event costs are front-loaded in the first year to align with the approach taken in the cost-effectiveness model

Estimated annual budget impact

Estimates of the expected budget impact of introducing nerandomilast for IPF are presented in Table 16 using patient access scheme (PAS) discounts for nerandomilast and nintedanib.

Estimates of the expected budget impact of introducing nerandomilast for PPF are presented in Table 17 using PAS discounts for nerandomilast and nintedanib.

The presented analyses account for the cumulative effect of patients having treatment for more than 1 year. The net budget impact is not expected to exceed the budget impact test of £40 million per year in any of the first 3 years of the analysis in either population.

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Table 16: Expected budget impact (PAS prices) – IPF

	Year 1 (£)	Year 2 (£)	Year 3 (£)	Year 4 (£)	Year 5 (£)
Total patients starting treatment	5,980	6,040	6,101	6,162	6,224
Population expected to initiate nerandomilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World without nerandomilast (total cost of current treatment pathway)					
Acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment monitoring costs (LFM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supplemental oxygen therapy costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End-of-life costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of current treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World with nerandomilast (total cost of future treatment pathway)					
Acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Year 1 (£)	Year 2 (£)	Year 3 (£)	Year 4 (£)	Year 5 (£)
Treatment monitoring costs (LFM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supplemental oxygen therapy costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End-of-life costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of future treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: IPF, idiopathic pulmonary fibrosis; LFM, liver function monitoring; PAS, patient access scheme.					

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Table 17: Expected budget impact (PAS prices) – PPF

	Year 1 (£)	Year 2 (£)	Year 3 (£)	Year 4 (£)	Year 5 (£)
Total patients starting treatment	897	906	915	924	934
Population expected to initiate nerandomilast	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
World without nerandomilast (total cost of current treatment pathway)					
Acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment monitoring costs (LFM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supplemental oxygen therapy costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End-of-life costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of current treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	Year 1 (£)	Year 2 (£)	Year 3 (£)	Year 4 (£)	Year 5 (£)
World with nerandomilast (total cost of future treatment pathway)					
Acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment monitoring costs (LFM)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supplemental oxygen therapy costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute exacerbation costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End-of-life costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of future treatment pathway	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: LFM, liver function monitoring; PAS, patient access scheme; PPF, progressive pulmonary fibrosis.					

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Updates to clarification question responses

Clinical parameters in the economic model

B6. <u>PRIORITY.</u> Section 3.3.5, Pages 166-167 (duration of continued treatment benefit following discontinuation).

Please provide further justification and information to support the assumption of one year of continued treatment benefit following discontinuation. Specifically, please:

- Provide additional data and/or analysis of the trial data to support this position. For example, please consider providing descriptive statistics detailing FVC measures at time points before and after treatment discontinuation.
- Consider additional statistical analyses to demonstrate the magnitude and/or duration of continued treatment benefit over time.

To address concerns in TA747 and TA864 about extrapolating indefinite benefit from short-term trial data, an explicit treatment waning framework was added for this technology appraisal in an effort to address uncertainties raised in previous technology appraisals.[5, 6] A similar concern was raised in the TA504 appraisal where the committee concluded that the evidence did not justify assuming a constant mortality benefit for 8 years after discontinuation, and that a constant benefit up to 5 years after discontinuation was a more reasonable assumption. Hence, the current submission employs an extremely conservative approach in comparison to previous economic models submitted to NICE, which limits the extrapolated treatment benefit for nerandomilast.

In the base case, waning is implemented as a step-change 1-year after the end of trial follow-up in the FIBRONEER trials (maximum follow-up in FIBRONEER-IPF and FIBRONEER-PPF: [redacted] and [redacted] years, respectively; the step-change is applied 1-year later, that is at [redacted] and [redacted] years from the start of the follow-up). Up to that point, any residual benefit is assumed to be captured through the extrapolation of the treatment effect estimates derived from the overall population. These extrapolations

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implicitly incorporate the impact of treatment discontinuations that occurred during the trial follow-up. After this 1-year post–follow-up period, patients who discontinue active treatment are assumed to receive no further continued benefit (follow BSC transition probabilities immediately). This conservative assumption avoids assuming continued long-term benefit where supporting evidence is not available. Because efficacy extrapolations for patients who remain on active treatment are derived from the overall trial population (so include the effects of observed treatment discontinuation) this approach will potentially underestimate the efficacy of active treatment.

Evidence to inform post-trial persistence of effect is limited because the FIBRONEER trials were not designed to estimate how long any benefit persists after treatment discontinuation. Across both FIBRONEER trials, follow-up is relatively short for informing long-term persistence, and the number of discontinuations is limited (Table 11). Furthermore, discontinuation is unlikely to be random as it may be related to underlying prognosis or changes in disease severity (e.g., tolerability issues, clinical deterioration, or other factors), meaning outcomes observed after stopping treatment could be confounded and difficult to interpret as an unbiased estimate of duration of benefit after discontinuation.

The post-trial period is where evidence becomes sparse, and there is no robust basis to quantify persistence of benefit beyond the observed follow-up, or to justify any specific duration of effect after discontinuation. In addition, the treatment effects of nerandomilast, nintedanib and pirfenidone are derived from analyses in the ITT population, and therefore already incorporate the impact of treatment discontinuations that occurred during the trials within the observed follow-up period. Given these limitations, we do not expect that additional analyses based solely on the FIBRONEER trial data would reliably estimate post-trial benefit persistence.

- Provide full details of each drug's half-life.

The reported terminal half-life for each drug are as follows:

- Approximately 10−17 hours for nerandomilast 18 mg bid[17]
- Between 10−15 hours for nintedanib[18]

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- Approximately 2.4 hours for pirfenidone[19]
- Provide detailed clinical validation of the assumption of a 1-year continued treatment benefit following treatment discontinuation.

As described above, the waning that was implemented a step-change 1-year after the end of trial follow-up in the FIBRONEER trials was done because the OS extrapolations implicitly incorporate the impact of treatment discontinuations that occurred during the trial follow-up. The model currently assumes no continued treatment benefit following treatment discontinuation beyond that time period – that is, people who discontinue nerandomilast more than 1-year from the end of trial follow-up are assumed to move directly to BSC efficacy. This is a conservative assumption, because the efficacy of nerandomilast is likely to persist for a short period after treatment discontinuation. This has been supported by clinical opinion in interviews with five English clinical experts and through structured expert elicitation (SEE) from 12 clinicians.[2, 20] All clinicians consulted acknowledged that the timing of loss of treatment effect is highly uncertain. At the same time, clinicians expected any benefit from nerandomilast to persist for a short period beyond treatment discontinuation.

Importantly, the estimates obtained from the SEE analysis also aligned with the base case assumption's mortality outputs that account for waning. For IPF, the modelled OS output lies within the interquartile range of the SEE estimates at both 5 and 15 years (Figure 6). For PPF, the modelled OS output is lower than the SEE estimates but remains within the plausible range, indicating conservative survival estimates in the model (Figure 7). Further details are provided in the SEE report available in the reference pack[20] and the SEE supplementary files submitted alongside these responses.

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Figure 6: Modelled OS output and SEE estimates – IPF



Key: BSC, best supportive care; IPF, idiopathic pulmonary fibrosis; OS, overall survival; SEE, structured expert elicitation.
Note: * Includes base case treatment waning assumption (no benefit assumed after the max FIBRONEER-IPF trial follow-up + 1 year; people who discontinue after this initial time period move directly to BSC efficacy)

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Figure 7: Modelled OS output and SEE estimates – PPF



Key: BSC, best supportive care; OS, overall survival; PPF, progressive pulmonary fibrosis; SEE, structured expert elicitation.
Note: * Includes base case treatment waning assumption (no benefit assumed after the max FIBRONEER-ILD trial follow-up + 1 year; people who discontinue after this initial time period move directly to BSC efficacy)

To support characterisation of the impact of uncertainty around the duration of treatment effect, additional scenarios are presented below that model treatment effect being lost from various timepoints:

- 50 years: approximates no loss of effect, consistent with the nintedanib appraisals[5, 6, 21] (Table 12 and Table 13)
- 5 years: consistent with the assumption made in the pirfenidone appraisal[22] (Table 14 and Table 15)

In summary, the waning that was implemented a step-change 1-year after the end of trial follow-up in the FIBRONEER trials was done because the OS extrapolations implicitly incorporate the impact of treatment discontinuations that occurred during the trial follow-up – to prevent any double-counting of discontinuation effects. A 1-

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year time period is a very conservative assumption compared with previous technology appraisals, especially as nerandomilast's efficacy is likely to persist for a short period after treatment discontinuation, as supported by UK clinicians, and which is currently not captured in the mode. Importantly, modelled mortality inclusive of treatment discontinuation is aligned with clinician expectations from interviews and the SEE, and the additional waning scenarios transparently bracket the plausible range around this reasonable central assumption.

Table 12: Fully incremental results with treatment effect lost at 50 years from model start – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	12,609	4.46	3.40	-	-	-	-
Pirfenidone	13,361	4.82	3.67	752	0.36	0.28	2,705
Nintedanib	[redacted]	4.82	3.67	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	9.21	6.80	[redacted]	4.39	3.12	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 13: Fully incremental results with treatment effect lost at 50 years from model start – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	17,458	4.65	3.32	-	-	-	-
Nintedanib	[redacted]	5.54	3.97	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	7.80	5.45	[redacted]	3.16	2.13	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

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Table 14: Fully incremental results with treatment effect lost at 5 years from model start – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	12,609	4.46	3.40	-	-	-	-
Pirfenidone	13,610	4.82	3.67	1,001	0.36	0.27	3,713
Nintedanib	[redacted]	4.82	3.66	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	6.63	5.03	[redacted]	1.82	1.36	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 15: Fully incremental results with treatment effect lost at 5 years from model start – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	17,458	4.65	3.32	-	-	-	-
Nintedanib	[redacted]	5.26	3.77	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	6.20	4.44	[redacted]	1.56	1.12	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Health state utility values

B7. Sections 3.4.7.1 and 3.4.7.2 (Pages 182-185) & Economic model, tab: "Utilities", Cell: "G56". Please confirm that when the switch for source of health state utilities is set to "FIBRONEER trial data", that this is applying utilities from the pooled analyses of the FIBRONEER-IPF and IMPULSIS studies for the IPF model and the pooled FIBRONEER-ILD and INBUILD studies for the PPF

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model. If so, please also provide utility values based on the FIBRONEER trial data alone for scenario analyses.

Thank you for bringing this to our attention. We confirm that when the source of health state utilities is set to 'FIBRONEER trial data' the model applies utility inputs derived from pooled analyses: FIBRONEER-IPF and INPULSIS for the IPF model, and FIBRONEER-ILD and INBUILD for the PPF model.

Utilities were pooled with INPULSIS and INBUILD because sample sizes within the FIBRONEER trials alone were small. When utilities were estimated using FIBRONEER trial data only, the resulting values were unstable and, for the IPF cohort, produced implausible estimates that were higher than general population utility. The utility values based on FIBRONEER trial data alone are provided in Table 16.

Table 16: Health state utilities from the FIBRONEER trials

FVC % predicted	FIBRONEER-IPF	FIBRONEER-ILD
≥ 110	[redacted]	[redacted]
100–109.9	[redacted]	[redacted]
90–99.9	[redacted]	[redacted]
80–89.9	[redacted]	[redacted]
70–79.9	[redacted]	[redacted]
60–69.9	[redacted]	[redacted]
50–59.9	[redacted]	[redacted]
40–49.9	[redacted]	[redacted]
30–39.9	[redacted]	[redacted]

Key: FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

Table 17 and Table 18 provide the results of the fully incremental analysis for IPF and PPF when using utility values from FIBRONEER only. The scenario has minimal impact on the fully incremental results: ICERs move only marginally versus the base case and the overall conclusions remain unchanged.

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Table 17: Fully incremental results using FIBRONEER-IPF utility values – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	12,609	4.46	3.31	-	-	-	-
Pirfenidone	13,625	4.74	3.52	1,016	0.28	0.21	4,824
Nintedanib	[redacted]	4.74	3.52	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	5.96	4.43	[redacted]	1.22	0.91	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 18: Fully incremental results using FIBRONEER-ILD utility values – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	17,458	4.65	3.37	-	-	-	-
Nintedanib	[redacted]	5.09	3.70	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	5.74	4.17	[redacted]	1.09	0.81	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

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B9. Section 3.4.6, Pages 181-182 (disutility of liver function tests). Please provide further details and justification for the application of a disutility for liver function tests in the economic model. Specifically, please:

- Provide further reassurance that this disutility has not already been captured by the health state utilities and that the risk of double-counting is minimal.

The health state utilities used in the economic model are derived from EQ-5D results from patients who participated in randomised controlled trials (RCT), specifically FIBRONEER-IPF, FIBRONEER-ILD, INPULSIS and INBUILD. It is widely acknowledged that that care received in an RCT setting is subject to rigorous quality standards with organised facilitation of diagnostic testing, medical support, and regular contact with a healthcare professional.[23, 24] RCT sites tend to also be located in urban areas at specialist centres and recruit patients within that geographic area; in a real-world setting, a significant proportion of patients IPF or PPF do not live within close proximity to specialist ILD centres, which contributes to the quality of life burden associated with these diseases.[25, 26] Therefore, the company is confident that the real-world quality of life impact (captured as a disutility in the economic model) associated with accessing liver function testing as part of the routine monitoring for patients receiving currently available antifibrotics (AF) is not captured in the health state utility values used in the economic modelling.

As described in Section 3.4.6 of the CS, it is on this basis that the company considers it appropriate to add an additional disutility for liver function testing in the economic model to quantitatively capture this lived reality for patients receiving current AF treatments for IPF and PPF. By not doing this, the company is concerned that the burden associated with liver function tests for patients with IPF and PPF will not be adequately reflected in the economic modelling and, therefore, miss a crucial aspect of the patient experience. The potential for nerandomilast to reduce liver function tests was repeatedly emphasised during clinical validation as one of the most meaningful differentiators in practice, given both patient burden and the operational implications for services.[2] Patients often describe ongoing monitoring as a ‘constant reminder of illness,’ contributing to treatment fatigue – an aspect not otherwise captured. Patients also consistently describe routine liver function tests as

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disruptive and anxiety-provoking, particularly when linked to treatment continuation or side-effect monitoring. While not altering underlying health status, these emotional and practical burdens meaningfully shape patients' lived experience and therefore justify a separate disutility.

- Comment on the validity of the assumption that the disutility of an IV infusion is generalisable to the patient experience of receiving a liver function test.

As described in the CS, no published evidence has been identified that directly quantifies a disutility associated with liver function testing. This evidence gap is expected, as the burden of monitoring procedures is rarely studied in isolation. However, patient feedback consistently highlights that regular monitoring obligations themselves – regardless of the procedure – carry emotional and logistical impact. This strengthens the rationale for applying a proxy disutility.

Therefore, an alternative source was used based on the intravenous (IV) infusion disutility used in TA898. The input used in TA898 included the disutility of three infusions but was adjusted for the economic modelling in this case to a single infusion to make this disutility generalisable to the patient experience of IPF and PPF. Although liver function tests are less intensive than infusions, both require healthcare attendance, scheduling, planning and generate anticipatory anxiety. Using a single-infusion disutility represents a conservative and proportionate estimate of monitoring burden without overstating impact.

The company acknowledges that there are limitations associated with this approach but in the absence of alternative evidence, considered this appropriate for inclusion in the company base case analysis.

To assess the impact of this input on the overall cost-effectiveness results, a scenario analysis has been conducted removing this disutility from the analysis.

Table 24 and Table 25 present the fully incremental results excluding liver function tests disutility. Excluding liver function tests disutility had minimal impact on results. As expected, only QALYs (and therefore ICERs) changed slightly, with no change to the fully incremental ordering or dominance conclusions.

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In IPF, the pirfenidone versus BSC comparison increased by 0.01 incremental QALYs (0.21 to 0.22), reducing the ICER from £4,831 to £4,533/QALY; nintedanib remained strictly dominated. The nerandomilast versus pirfenidone comparison decreased by 0.01 incremental QALYs (0.93 to 0.92), increasing the ICER marginally from [redacted] to [redacted]/QALY. In PPF, the nintedanib versus BSC comparison increased by 0.02 incremental QALYs (0.33 to 0.34), and nintedanib remained extendedly dominated versus BSC. The nerandomilast versus BSC comparison remained the same as the base case estimates ([redacted]/QALY).

Overall, the scenario changes were small and did not affect the existing conclusions.

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Table 24: Fully incremental results excluding liver function tests disutility – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	12,609	4.46	3.40	-	-	-	-
Pirfenidone	13,625	4.74	3.62	1,016	0.28	0.22	4,533
Nintedanib	[redacted]	4.74	3.62	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	5.96	4.54	[redacted]	1.22	0.92	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 25: Fully incremental results excluding liver function tests disutility – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	17,458	4.65	3.32	-	-	-	-
Nintedanib	[redacted]	5.09	3.66	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	5.74	4.12	[redacted]	1.09	0.80	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

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Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of the company submission.

A template is provided by NICE. This template is adapted from the International SIP template from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open access IJTAHC journal article.

The purpose of the SIP

The purpose of the SIP is to provide patients and patient groups involved in providing input to the HTA evaluation, with relevant and appropriate information on the medicine collected and summarised in one document. Patients will use the information provided in the SIP as an important resource as they consider their own input into the HTA evaluation. The SIP is not intended to replace a patient or patient group's own information gathering, but to complement it.

The SIP may also serve as a useful resource for any other stakeholders that appreciate a plain language summary of the medicine and its benefits and risks.

How to complete the SIP

The information in the template should not include any confidential information and will be published alongside the other committee papers on the NICE public website.

All information provided should be factual and presented in a balanced way. It should fairly represent the body of evidence available and the medicine's benefit/risk profile.

Where possible, diagrams or infographics should be used to help make the information patient friendly, with accompanying text for accessibility.

The use of technical or scientific jargon should be avoided, but if scientific terminology cannot be avoided, it should be explained at first use. Short sentences and simple sentence structure should be applied throughout.

A completed SIP should not exceed 20 pages including all references.

Testing of the SIP

It is recommended that wording and language is tested with a lay reader or patient / patient group before submission, to ensure the summary is suitable for the audience.

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Generic name: Nerandomilast Brand name: JASCAYD®

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

People who are 18 years or older (adults) with idiopathic pulmonary fibrosis (IPF) or progressive pulmonary fibrosis (PPF).

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The marketing authorisation for nerandomilast is pending – please see Section 1.2 of the company submission for anticipated dates of approval.

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Between 2023 and to date, Boehringer Ingelheim worked with several patient organisations that support people with interstitial lung disease (ILD) or conditions that can lead to ILD. These collaborations helped ensure that the experiences of people living with ILD and related conditions informed our research, study documents and educational activities. The activities below reflect the nature and

purpose of these engagements, including where no financial support was provided.

Action for Pulmonary Fibrosis (APF)

Nature of collaboration: Contracted insight work, participation in ILD meetings and workshops, and community-focused support.
Reason for engagement: APF represents people affected by pulmonary fibrosis and provides essential insight into daily challenges, unmet needs and communication preferences.
Purpose of activities:

- Review patient information sheets and consent forms to ensure clarity
- Provide patient perspectives during early study planning (clinical trials and real-world evidence studies)
- Take part in ILD educational and pathway workshops such as OneVoice ILD and ILD Academy Live
- Support surveys, focus groups and wider PPI activities (2025)

Financial support: Contracted insight work and a grant supporting ILD community involvement.

National Rheumatoid Arthritis Society (NRAS)

Nature of collaboration: Contracted insight related to ILD that can occur in rheumatoid arthritis.
Reason for engagement: Some people with rheumatoid arthritis develop ILD; NRAS provides patient perspectives relevant to this group.
Purpose of activities:

- Input on study plans to reflect the needs of people with RA-associated ILD
- Participation in ILD pathway discussions and ILD Academy Live
- Support for an ILD-related patient survey

Financial support: Contracted insight work and support for participation in workshops.

Scleroderma & Raynaud's UK (SRUK)

Nature of collaboration: Contracted insight and grant-supported activity.
Reason for engagement: Lung involvement is common in scleroderma, making SRUK an important voice for patients with autoimmune-related ILD.
Purpose of activities:

- Provide patient insight for early study planning and protocol development (clinical studies and real-world evidence studies)

- Support activities to improve understanding of ILD as part of scleroderma care

Financial support: Contracted insight work and a healthcare-specialist grant

The Neurological Alliance

Nature of collaboration: Participation in ILD multi-stakeholder discussions.
Reason for engagement: To provide cross-condition patient experience relevant to navigating complex care pathways.
Purpose of activities:

- Contribute lived-experience perspectives to OneVoice ILD meeting discussions

Financial support: Participation support only; no broader collaboration.

Pulmonary Fibrosis Trust (insight only, non-financial)

Nature of engagement: Informal, non-contracted discussions to gather insight.
Reason for engagement: To understand real-life experiences of people living with IPF.
Purpose:

- Gain insight into daily living, emotional impact and support needs
- Ensure understanding of these challenges informs patient-centred research and communication

Financial support: None

Bolton Pulmonary Fibrosis Support Group (insight only, non-financial)

Nature of engagement: Informal insight-gathering meetings.
Reason for engagement: To hear directly from people with pulmonary fibrosis in a community setting.
Purpose:

- Understand experiences around diagnosis, breathlessness, family impact and support needs

Financial support: None.

Asthma & Lung UK (insight only, non-financial)

Nature of engagement: Partnership work to jointly develop a national ILD report for Scotland, including co-development of a national ILD pathway and a consensus statement. This collaboration also contributed to a parliamentary event at Holyrood. No payment was made, and no formal contracted activity took place.

Reason for engagement: To ensure the national ILD pathway and related recommendations were informed by the real-world experiences of people affected by ILD across Scotland, and to support broader understanding of ILD challenges within NHS Scotland and Scottish Government settings.

Purpose:

- Co-develop a report highlighting key issues, unmet needs, and opportunities for improving ILD care in Scotland
- Collaborate on establishing a national ILD pathway and consensus recommendations informed by clinical and patient input
- Support preparation for a parliamentary event at Holyrood, helping raise awareness of ILD at national policymaking level

Financial support: None. No payment, no contracted work, and no commissioned activity.

Section 2: current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF) are long-term (chronic) lung conditions that worsen over time (progress).[1-3] In both conditions, the lungs are damaged by an abnormal healing process. Normally, when the lungs are injured, the body repairs the damage and then stops. In IPF and PPF, this repair process does not switch off. As a result, there is ongoing swelling (inflammation) and build-up of scar tissue in the lungs (fibrosis).[4-6] This scarring makes the lungs stiff and less able to expand, which makes breathing harder, It also reduces the amount of oxygen that can pass from the lungs into the blood.[4-6] Once lung tissue is scarred, it cannot be repaired. Treatments may slow the disease, but they cannot stop it. IPF and PPF continue to worsen over time. These conditions have a major impact on daily life and significantly shorten life expectancy.[1, 3]

In the UK, around 7,000 new cases of IPF and PPF are diagnosed each year with IPF affecting around 10 per 100,000 people and PPF affecting around 1.5 per 100,000 people.[7, 8] The course of the disease can vary from person to person, but most people experience a steady decline in lung function and around 55% of patients are not expected to live for more than 5 years following a diagnosis of IPF

or PPF, despite treatment.[1, 3] In the UK, more than 5,000 people die from IPF each year, which means that IPF causes around 1% of all UK deaths.[9, 10]

The early signs of IPF or PPF often include unexplained shortness of breath during activity, a persistent dry cough, crackling sounds in the lungs when breathing in, and changes to the shape of the fingertips or toenails, known as clubbing.[11-13] As the disease progresses, breathlessness and coughing usually become worse, and everyday tasks may become more difficult.[1, 14, 15] Many people eventually need oxygen therapy to help them breathe.[1, 14] Severe tiredness (fatigue) is also common and can lead to loss of independence and social isolation, which in turn may cause feelings of depression.[1, 16, 17]

Anxiety and depression are often reported by people affected by IPF or PPF and their carers, given the unpredictable and ultimately progressive nature of the disease and the limited treatment options available (see Section 2c).[16]

It is also common for people with IPF or PPF to have other health problems alongside their lung disease. In the UK, up to 84% of people with IPF or PPF have at least one other condition, such as high blood pressure, heart disease, acid reflux, or diabetes.[18-20] These additional health issues can add to the challenges of living with IPF or PPF.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

In the UK, people with IPF and PPF are usually diagnosed, assessed, and treated in specialist interstitial lung disease (ILD) centres.[21]

Diagnosis is often complex and involves a team of clinical experts, plus breathing tests, detailed lung scans, and sometimes a lung biopsy (removal of a small piece of lung tissue for laboratory examination).[22] Diagnosis of IPF is anchored to a specific pattern of lung injury with an unknown cause (idiopathic), whereas diagnosis of PPF is anchored to an existing ILD of a known or unknown cause (other than IPF), along with evidence of worsening of disease.[22]

Diagnosis of IPF and PPF is often delayed because early symptoms like breathlessness, cough, and severe tiredness (fatigue) can be mistaken for other illnesses.[2, 21, 23, 24] From first symptoms to a confirmed diagnosis, the total delay is typically around 6 to 12 months (data on file), although it can be longer with some patients experiencing symptoms for more than 2 years before their first visit to an

ILD centre.[20] Treatment thus may not begin until well after the disease has started to progress.[25, 26] Some people feel that access to specialist care and testing is too slow, and a few have even said they would prefer the faster, clearer pathways available for cancer diagnoses (see Section 2d).[1]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are

For IPF, the National Institute for Health and Care Excellence (NICE) currently recommends two antifibrotic (AF) medicines – nintedanib and pirfenidone.[27-29] For PPF, nintedanib is the only NICE-recommended active treatment.[30] Before PPF is formally diagnosed, care is usually aimed at treating the underlying cause of the lung disease. This may include medicines to reduce inflammation.

Although AF medicines have been available for around 10 years and can help slow down the worsening of lung function for some people with IPF or PPF, treatment options are still limited. Currently available AF therapies are not suitable for everyone i.e. nintedanib is not suitable for people with a soya allergy and pirfenidone use in the UK is limited to a subgroup of people with IPF with a certain lung capacity range (forced vital capacity [FVC] 50–80% predicted). In addition, current AF medicines should be taken with meals adding complexity to how people manage their disease.

Unfortunately, despite treatment, life expectancy remains poor (see Section 2a) which shows that current medicines are not strong enough to control IPF or PPF over the long-term.[3]

AF medicines can also cause unpleasant side effects, particularly diarrhoea.[31-33] These can be difficult to manage and often mean that people need to reduce their dose or stop treatment altogether.[31-33] When this happens, it can limit how well the current medicines work and reduce the chance of getting lasting benefit.

In both IPF and PPF, everyone is offered best supportive care (BSC). This can be given alongside AF medicines, or on its own if active treatment is not possible.[34, 35] BSC focuses on helping people feel as well as they can by managing symptoms, providing oxygen therapy, offering pulmonary rehabilitation, treating other health conditions, and ensuring access to palliative and emotional support.[34, 35]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

A large UK survey carried out by Action for Pulmonary Fibrosis (APF) in 2023 showed that a diagnosis of IPF and PPF can have a sizeable physical and emotional impact.[1] People reported that the rapid worsening of symptoms – especially severe breathlessness and the loss of ability to stay active – has a major effect on mental wellbeing and day-to-day quality of life. The emotional impact often extends beyond the person diagnosed, affecting partners, caregivers and loved ones. One person living with IPF described their experience in a powerful way: *"Breathlessness can feel like having a 25 kg sack of sand tied around your chest. You cough a thousand times a day, you can't find your next word, you stumble out of exhaustion, you feel like a zombie"*. This quote reflects the profound burden that many people with IPF and PPF face – a combination of physical limitations, exhaustion, and the emotional strain of coping with a progressive condition. Additionally, several people in the survey said they would

prefer to have a cancer diagnosis, citing a lack of support within the healthcare system and delays in getting diagnosed.

The survey also captured the emotional toll of the disease, with respondents using words such as "*depressed", "anxious", "stressed", "not coping", "isolated", "worried", "scary*", and "*alone*". As part of APF's *Every Breath Counts* campaign, people with IPF or PPF (and their caregivers) used words such as *"unfair," "horrific," "cruel," and "relentless,"* reflecting the substantial physical and emotional burden of the disease.[36-40]

Concerns raised in the APF survey were echoed by patient experts at previous NICE Committee meetings, who described how IPF and PPF severely affects mobility, mental health, and the ability to carry out daily activities.[29] The burden extends beyond people affected by IPF/PPF to those who care for them. A Delphi panel found that 85–90% of experts agreed that unpaid caregivers of people with PPF experience reduced quality of life, especially in areas such as sleep, emotional wellbeing, daily activities, social life, and financial stability.[41]

The need for oxygen therapy can cause further stress and anxiety for people living with IPF or PPF and their caregivers.[1, 14, 42] People have described being on long-term oxygen at home as feeling like being *"on a leash"*, with equipment creating potential hazards in their living space.[1, 14, 42]

Section 3: the treatment

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

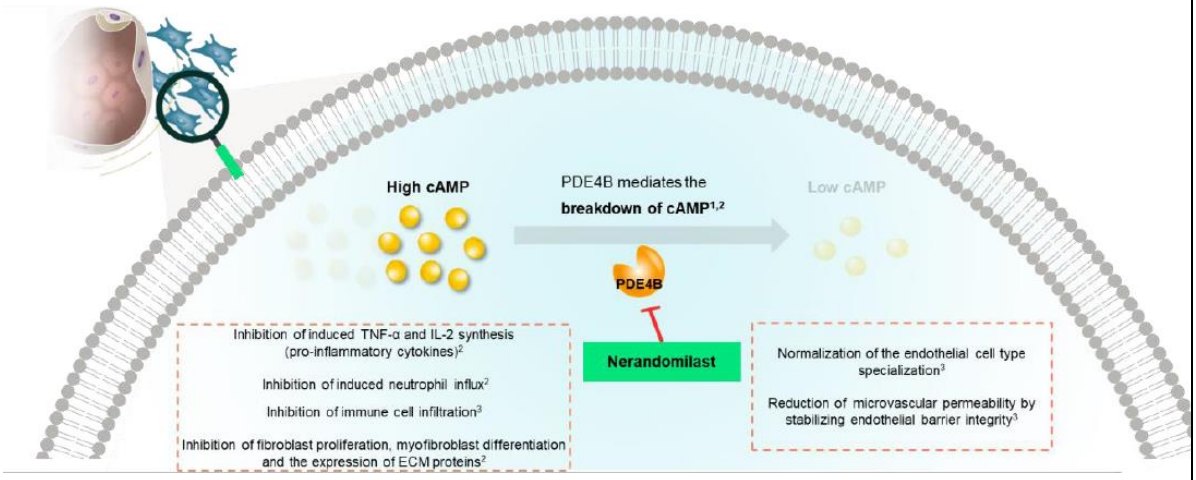
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Nerandomilast is a medicine designed to block an enzyme called phosphodiesterase 4B (PDE4B), which is found in high amounts in the lungs and in certain immune cells. This enzyme plays a role in both inflammation and in the development of scar tissue (fibrosis).[43-45] Scar tissue makes the lungs

stiff, which makes breathing harder and reduces how much oxygen can get into the bloodstream.[4-6] By blocking PDE4B, nerandomilast may help reduce inflammation in the lungs, slow or prevent the build-up of scar tissue and support healthier lung tissue function. It may also help harmful scar-producing cells to die naturally and reduce the proteins that contribute to scarring (Figure 1). Together, these effects may help protect lung function and slow the progression of IPF or PPF.

Figure 1: Mechanism of action



Key: cAMP, cyclic adenosine monophosphate; ECM, extracellular matrix; IL-2, interleukin-2, PDE4B, phosphodiesterase 4B; TNF-α, tumour necrosis factor alpha.
Source: Reininger et al. 2024[46]; Herrmann et al. 2022[43]; Kolb et al 2023.[44]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Nerandomilast is designed to be used on its own (monotherapy), not together with currently available AFs (nintedanib or pirfenidone). It can be used as an ‘add-on’

treatment to BSC. For people with PPF, this may include treatments such as immunosuppressant medicines to help manage the underlying lung condition.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Nerandomilast treatment is prescribed in specialist ILD centres but can be taken at home as it is available in tablet form.

Two tablets are to be taken per day; one in the morning and one in the evening, and they can be taken with or without food.

The normal dose of each tablet is 18 mg, but 9 mg tablets are also available for people who need a lower daily dose.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The main clinical trials providing evidence for the use of nerandomilast are FIBRONEER-IPF (NCT05321069) for people with IPF and FIBRONEER-ILD (NCT05321082) for people with PPF.[47, 48]

The FIBRONEER trials were designed to find out how well nerandomilast works compared with placebo (a replica tablet with no active medicine), in people with IPF or PPF, and how safe it is.[47, 48]

FIBRONEER-IPF and FIBRONEER-ILD took place across multiple treatment centres, including sites in the UK.[49, 50] Both participants and researchers were ‘blinded’ to treatment, meaning they did not know which participants were given nerandomilast or placebo. In FIBRONEER-IPF 1,177 patients with IPF were randomised in a 1:1 ratio to receive nerandomilast or placebo; of these 87 participants were treated with nerandomilast 18 mg twice a day (bid) monotherapy and 87 participants were treated with placebo monotherapy.[48] In FIBRONEER-ILD,

1,178 patients with PPF were randomised in a 1:1 ratio to receive nerandomilast or placebo; of these, 220 participants in FIBRONEER-ILD were treated with nerandomilast 18 mg bid monotherapy and 222 participants were treated with placebo monotherapy.[47] Monotherapy means that participants that were not receiving any background AF therapy alongside randomised treatment (nerandomilast or placebo).[47, 48]

To be included in FIBRONEER-IPF, participants had to:[48]

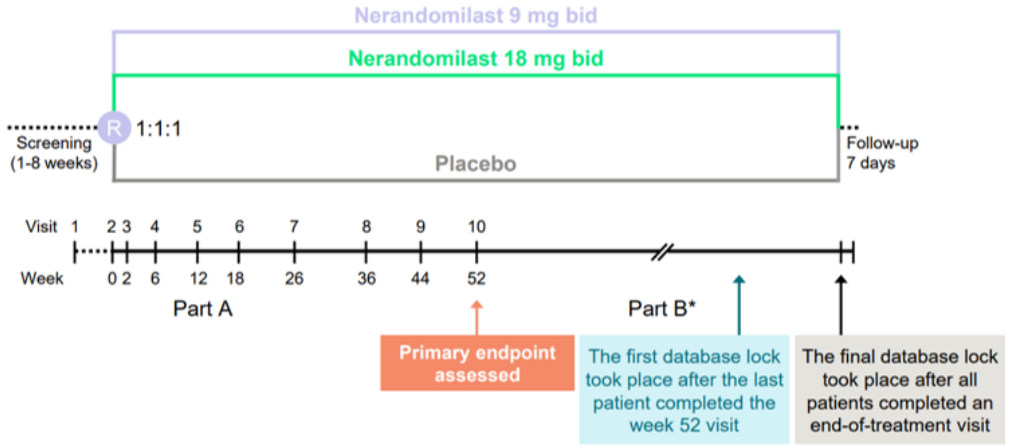
- Have a confirmed IPF diagnosis based on national and international guidelines. This was determined from a high resolution computed tomography (HRCT) scan taken within the past 12 months, showing a pattern called usual interstitial pneumonia (UIP) or probable UIP, which matches the typical appearance of IPF
- Be aged 40 or over
- Have a minimum level of lung function. This meant:
  - Their lung capacity must be at least 45% of what is considered normal for someone of the same age, sex, and body size (assessed by FVC)
  - Their lungs must be able to transfer oxygen into the blood at least 25% of the normal level (assessed by diffusing capacity of the lungs for carbon monoxide [DL_{CO}])
- Current treatment status – be either on a stable dose of nintedanib or pirfenidone for at least 12 weeks before the study, or not taking either medication for at least 8 weeks before joining the study

To be included in FIBRONEER-ILD, participants had to:[47]

- Have a confirmed PPF diagnosis – based on HRCT scans (within 12 months of screening) reviewed centrally, showing fibrotic (scarred) lung changes and evidence of disease progression within the past 24 months. Progression was defined by a combination of:
- A clinically meaningful decline in lung capacity (i.e. FVC)
  - Worsening respiratory symptoms, such as increased shortness of breath, and
  - More scarring in the lungs seen on scans
- Be 18 years or older
- Have a minimum level of lung function (as in the FIBRONEER-IPF trial)
- Treatment status – be on a stable dose of nintedanib for at least 12 weeks before screening, or not taking nintedanib for at least 8 weeks before screening
- Use of immunosuppressive medicines – be on a stable dose of permitted immunosuppressive drugs (other than corticosteroids) for the underlying disease for at least 12 weeks before screening and during the screening period

An overview of the FIBRONEER trials study design is depicted in Figure 2.

Figure 2: Study design overview for FIBRONEER-IPF and FIBRONEER-ILD



Key: bid, twice a day; CTR, clinical trial report; R, randomised.
Notes: * Visits occurred every 12 weeks until the last participant completed 52 weeks of treatment.
Source: adapted from Maher et al. 2025[47] and Richeldi et al. 2025.[48]

The trials are complete, with the main analysis performed after the last randomised participant had completed the Week 52 assessment (16 August 2024 in FIBRONEER-IPF and 18 December 2024 in FIBRONEER-ILD)[47, 48] and the final analysis performed after the last participant had completed the trial (data on file).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Primary endpoint: Absolute change from baseline in FVC (mL)

In FIBRONEER-IPF and FIBRONEER-ILD, the main goal was to measure how participants' lung capacity changed over time.[47, 48] This measurement is called the absolute change from baseline FVC. FVC is the total amount of air a person

can blow out after taking the deepest breath possible. Comparing FVC results from the start of the study to later measurements shows whether breathing ability has improved, stayed the same, or declined.

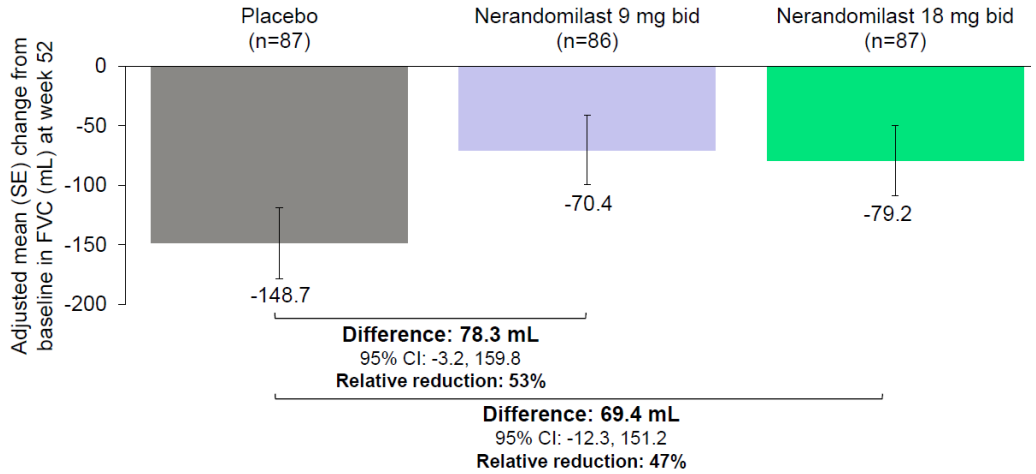
The primary endpoint was met in both trials, with a statistically significant benefit in reduction in lung function at 52 weeks with nerandomilast treatment in the overall trial population (nerandomilast given with or without background AF therapy).[47, 48]

FIBRONEER-IPF

The lung function of participants treated with nerandomilast 18 mg bid monotherapy declined 47% less over 52 weeks compared with placebo (Figure 3). On average, participants receiving nerandomilast 18 mg bid monotherapy lost about 79 mL of lung capacity, while those on placebo lost about 149 mL.[48]

Early onset and sustained treatment effect was observed with nerandomilast 18 mg bid monotherapy; over the total trial duration, participants receiving nerandomilast 18 mg bid monotherapy lost lung capacity at about half the rate of those on placebo (data on file).

Figure 3: Change from baseline in FVC (mL) at Week 52, FIBRONEER-IPF ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; CI, confidence interval; FVC, forced vital capacity; SE, standard error.
Source: Adapted from Richeldi et al. 2025.[48]

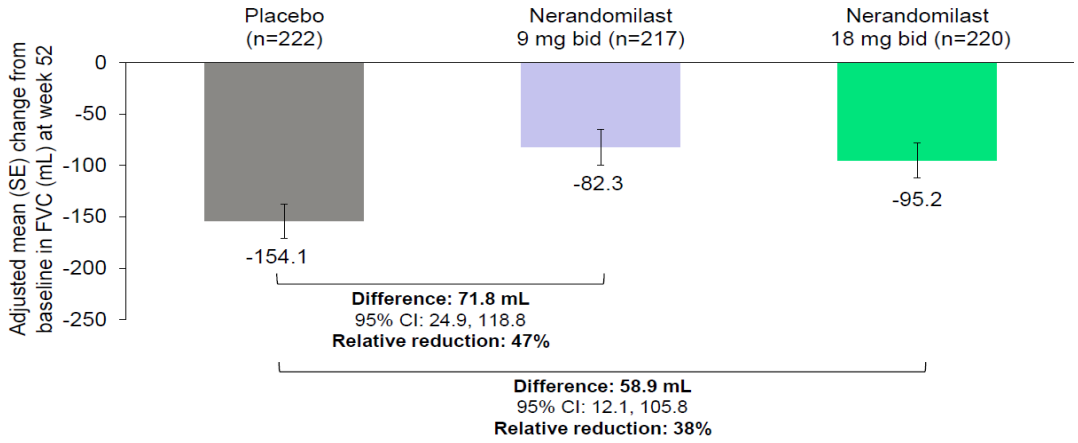
FIBRONEER-ILD

Lung function of participants treated with nerandomilast 18 mg bid monotherapy declined about 38% less over 52 weeks compared to placebo (Figure 4). On average, participants receiving nerandomilast 18 mg bid monotherapy lost about 95 mL of lung capacity, while those on placebo lost about 154 mL.[47]

As compared to baseline, an unprecedented improvement in lung function was observed in the first few months of treatment with nerandomilast 18 mg bid

monotherapy and a higher treatment effect versus placebo was observed over the total trial duration (data on file).

Figure 4: Change from baseline in FVC (mL) at Week 52, FIBRONEER-ILD ('no AF background therapy' cohort)



Key: AF, antifibrotic; bid, twice a day; CI, confidence interval, FVC, forced vital capacity; SE, standard error.
Source: Adapted from Maher et al. 2025.[47]

FIBRONEER-IPF and FIBRONEER-ILD pooled results

When data from both FIBRONEER studies were combined, participants treated with nerandomilast 18 mg bid monotherapy experienced a significantly slower decline in lung function over 52 weeks compared with those on placebo (data on file).

Key secondary endpoint: Time to the first occurrence of acute IPF/ILD exacerbation, first hospitalisation for respiratory cause or death over the duration of the trial

In both studies, another important goal was to track how long it took for any of the following to happen for the first time:[47, 48]

- An acute exacerbation event
- Hospitalisation for a respiratory cause, or
- Death from any cause during the study

An acute exacerbation event means a sudden and severe worsening of breathing symptoms.[51] These events are linked to accelerated disease progression and increased risk of death.[52-54]

The key secondary endpoint was not met in either trial, with no statistically significant difference in the composite endpoint over the duration of the trial with

nerandomilast treatment in the overall trial population (nerandomilast given with or without background AF therapy).[47, 48]

FIBRONEER-IPF

Up to the end of the study, participants receiving nerandomilast 18 mg bid monotherapy showed a clinically meaningful benefit in the combined measure of time to the first acute IPF exacerbation, first hospitalisation for a respiratory cause, or death from any cause (data on file). Importantly, participants receiving nerandomilast 18 mg bid monotherapy had a lower risk of dying than those taking placebo (data on file).

FIBRONEER-ILD

Up to the end of the study, participants receiving nerandomilast 18 mg bid monotherapy showed a considerable benefit in the combined measure of time to the first acute ILD exacerbation, first hospitalisation for a respiratory cause, or death from any cause (data on file).

Participants receiving nerandomilast 18 mg bid monotherapy showed a benefit in four out of five individual measures that make up the combined secondary outcome (data on file). Compared with placebo, they had a lower risk of acute ILD exacerbation or death, respiratory-related hospitalisation or death, respiratory-related hospitalisation alone, and death (data on file). The greatest reduction in risk was seen for death.

FIBRONEER-IPF and FIBRONEER-ILD pooled results
When data from both FIBRONEER studies were combined, participants receiving nerandomilast 18 mg bid monotherapy experienced significantly fewer respiratory events compared with those on placebo over the total trial duration (data on file).

Treatment with nerandomilast 18 mg bid monotherapy extended the participants' total lifetime and the time they lived without disease progression, represented by an FVC % predicted decline of ≥10% (data on file).

Secondary endpoint: Use of supplemental oxygen

Over the duration of both the FIBRONEER-IPF and FIBRONEER-ILD trials, fewer participants receiving nerandomilast 18 mg bid monotherapy needed oxygen therapy to help them breathe compared with those receiving placebo therapy (data on file).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Participants' quality of life was assessed using the following validated questionnaires:[47, 48]

- Living with Pulmonary Fibrosis (L-PF) questionnaire. The L-PF questionnaire is a self-administered, 44-item questionnaire that focuses on participant symptoms (dyspnoea, cough and fatigue) and the impact of these symptoms on the participant. The questionnaire's summary scores range from 0 to 100, with a higher score indicating greater impairment
- The EuroQol-5 Dimension Visual Analog Scale (EQ-5D-5L VAS). The EQ-5D-5L is a standard questionnaire used in health research to measure quality of life. It asks about five areas of daily living – mobility, self-care, usual activities, pain/discomfort, and anxiety/depression – and also uses a visual scale where patients rate their overall health from 0 (worst imaginable health) to 100 (best imaginable health)

L-PF (FIBRONEER-IPF)

Over 52 weeks, participants receiving nerandomilast 18 mg bid monotherapy had slightly less worsening in daily life impact and symptoms compared with those receiving placebo (data on file).

L-PF (FIBRONEER-ILD)

Similar findings were observed in people with PPF; participants receiving nerandomilast 18 mg bid monotherapy showed slightly less worsening over 52 weeks than those on placebo (data on file).

EQ-5D (FIBRONEER-IPF/FIBRONEER-PPF)

In both the FIBRONEER studies, changes in EQ-5D scores over the total trial duration were similar between participants receiving nerandomilast 18 mg bid monotherapy and those on placebo (data on file).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, nerandomilast can cause side effects, although most are considered mild in nature and medically manageable. Possible side effects of nerandomilast include:

- Diarrhoea
- Weight loss
- Decreased appetite
- Nausea
- Back pain

In the FIBRONEER trials, the safety of nerandomilast was measured by recording the number and type of treatment-emergent adverse events (TEAEs), defined as any side effects that started any time from the first dose of the trial medication to 7 days after the last dose.[47, 48]

While nearly all participants receiving nerandomilast 18 mg bid monotherapy across both FIBRONEER trials experienced a TEAE, nerandomilast 18 mg bid was associated with a lower rate of serious TEAEs, TEAEs leading to permanent

treatment discontinuation, and fatal TEAEs (serious TEAEs resulting in death) compared with placebo.[47, 48]

Across the FIBRONEER studies, the most commonly reported TEAEs with nerandomilast 18 mg bid monotherapy included diarrhoea, respiratory infections, and cough.[47, 48] Most diarrhoea AEs reported were mild in intensity (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1, i.e. increase of < 4 stools/day), with no Grade 3 or higher diarrhoea AEs reported in FIBRONEER-IPF or in FIBRONEER-ILD over the duration of the trial with nerandomilast 18 mg bid monotherapy (data on file).

Key safety outcomes at the time of the main analysis are summarised in Table 1.

Table 1: Treatment-emergent adverse events in the monotherapy population of the FIBRONEER trials

n (%)	FIBRONEER-IPF		FIBRONEER-ILD	
	NERA 18 mg bid (N = 87)	**Placebo (N = 87)**	**NERA 18 mg bid (N = 220)**	**Placebo (N = 222)**
Any TEAE	79 (90.8)	85 (97.7)	203 (92.3)	207 (93.2)
Serious TEAE	23 (26.4)	31 (35.6)	80 (36.4)	98 (44.1)
TEAE leading to tx discontinuation	11 (12.6)	7 (8.1)	21 (9.5)	28 (12.6)
Fatal TEAE	0	8 (9.2)	5 (2.3)	16 (7.2)
Common TEAEs:				
Diarrhoea	23 (26.4)	7 (8.1)	59 (26.8)	35 (15.8)
URTI	13 (14.9)	8 (9.2)	34 (15.5)	46 (20.7)
Cough	9 (10.3)	4 (4.6)	37 (16.8)	32 (14.4)

Key: IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; TEAE, treatment-emergent adverse event; tx, treatment; URTI, upper respiratory tract infection.
Source: Maher et al. 2025[47]; Richeldi et al. 2025.[48]

Clinical experts described the overall safety profile of nerandomilast as manageable and potentially more favourable than that of existing AF treatments (data on file). Side effects such as diarrhoea occurred at rates expected for medicines in the same class (PDE4 inhibitors) and were not considered excessive. Experts noted that the medicine's dose-dependent tolerability – and the option to reduce the dose without losing its effectiveness – is a practical advantage, as it allows clinicians to manage side effects more easily while maintaining treatment benefits.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Nerandomilast is the first preferential inhibitor of PDE4B with AF and immunomodulatory properties for people with IPF or PPF.

The key benefits of nerandomilast compared with BSC are represented by the placebo comparisons in the FIBRONEER trials as presented in Section 3e.

The key benefits of nerandomilast compared with AF therapy have been investigated in patient-level data analyses of the FIBRONEER trials and nintedanib trials (INPULSIS for IPF and INBUILD for PPF) (data on file). These analyses showed:

- Similar lung protection: Nerandomilast slowed the loss of lung function at about the same rate as current treatment
- Lower risk of death: Nerandomilast reduced the risk of death compared to current treatment
- Fewer stomach and bowel side effects: Nerandomilast reduced the chance of experiencing diarrhoea or other gastrointestinal side effects compared to current treatment
- Lower chance of stopping treatment due to side effects: Nerandomilast reduced the chance of people having to stop treatment due to side effects
- Staying on treatment longer: People were able to continue nerandomilast for a longer period before stopping it, compared with nintedanib

Additionally, there is no need for regular liver function blood tests to check for possible liver injury with nerandomilast as compared to current AF medicines (nintedanib and pirfenidone).[55-57] These tests, which are required when using nintedanib or pirfenidone, mean frequent trips to healthcare centres, which can be difficult for people with mobility problems, severe breathlessness, or who live far from specialist clinics. Many patients say the travel, managing oxygen equipment, and fatigue add extra strain, and for some, this has discouraged continuing treatment (data on file).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Nerandomilast, like all medicines, can cause side effects, but as noted above, common side effects are generally mild in nature and medically manageable.[47, 48] In the FIBRONEER trials, there was no increase in side effects with nerandomilast treatment compared with best supportive care (see Section 3g) and nerandomilast was shown to have a lower risk of side effects and having to stop treatment due to side effects compared with current AF treatment (see Section 3h).

Importantly, the side effects observed in the FIBRONEER trials did not negatively impact participant quality of life within the studies and rarely resulted in dose reductions or stopping of treatment which would limit the potential clinical benefit of nerandomilast.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

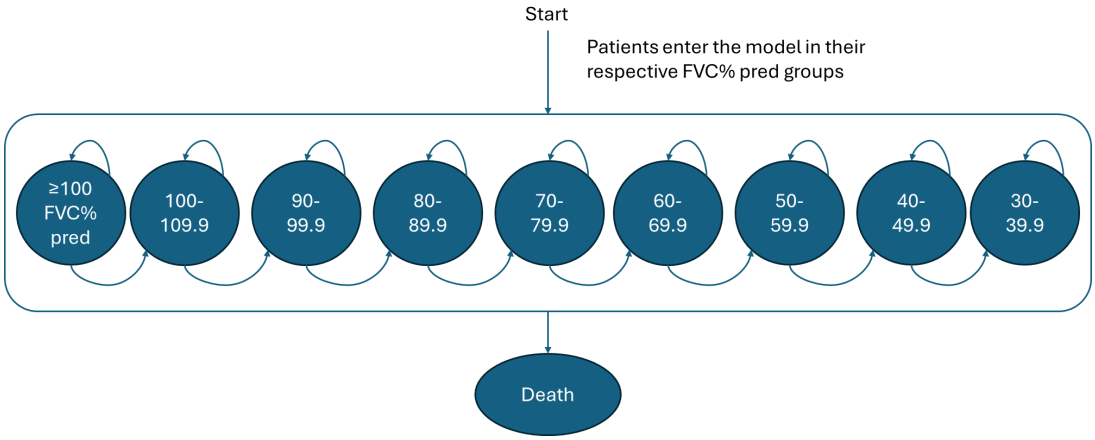
- The extent to which you agree/disagree with the value arguments presented below (e.g. whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g. travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments, affects your quality of life

Cost-effectiveness model approach

A cost-effectiveness model was developed to assess the economic value of using nerandomilast compared with the current treatment options – BSC, nintedanib or pirfenidone – to the National Health Service and personal social services (NHS and PSS). The same model allows users to consider either IPF or PPF. It shows disease progression as a series of stages (health states) based on lung function, measured in steps of FVC decline of 10% predicted (Figure 5).

Figure 5 Cost-effectiveness model structure



Key: FVC, forced vital capacity; pred, predicted.

This model uses information from large clinical studies to understand how lung disease may change over time with different treatments. It looks at results from the FIBRONEER studies (for nerandomilast and best supportive care) and compares them with other studies of existing treatments (INPULSIS for IPF and INBUILD in PPF for nintedanib. Pirfenidone is assumed equal to nintedanib for most clinical inputs).

Using this information, the model estimates how quickly a person's condition may progress through different stages of illness (also called a 'health state'). Each stage is linked to expected healthcare costs and to how people feel and function in daily life. Quality of life is measured using a patient questionnaire (EQ-5D) completed during the clinical studies.

The model then combines how long a person is likely to spend in each stage with their quality of life during that time. This helps estimate the overall benefit a treatment provides, taking into account both length and quality of life.

Finally, this information is used to understand whether the benefits (measured as the total number of quality-adjusted life years (QALYs) gained) people gain from treatment with nerandomilast are reasonable when compared with the overall costs of treatment for conditions like IPF or PPF.

Clinical benefits included in the model

The model suggests that people taking nerandomilast are likely to live longer than those taking other available treatments (Table 2). Living longer is the main contributor to the QALY gain observed. Additional QALY benefits stem from the fact that nerandomilast is generally easier to tolerate than other treatments. People taking nerandomilast are less likely to stop treatment because of side effects, and their lung function tends to decline more slowly.

Together, these factors mean that nerandomilast may help people live both longer and better lives compared with other treatments.

Table 2: Summary of life years and QALYs results

Nerandomilast compared with:	Additional life years:		Additional QALYs:	
	IPF	PPF	IPF	PPF
BSC	1.50	1.09	1.14	0.80
Nintedanib	1.22	0.47	0.93	0.35
Pirfenidone	1.22	N/A	0.93	N/A

Key: BSC, best supportive care; IPF, idiopathic pulmonary fibrosis; LY, life years; N/A, not applicable; PPF, progressive pulmonary fibrosis; QALY, quality-adjusted life year.

Costs included in the model

The following cost categories are included in the model:

- Treatment costs: Costs of acquiring treatment are applied for all people while receiving nerandomilast, nintedanib or pirfenidone
- Treatment management: Liver function testing costs are applied for people receiving nintedanib and pirfenidone
- Disease management: Costs are applied for all alive people with costs dependent on the patients' FVC % predicted
- AE management: Costs are applied at the beginning of the model for people receiving nerandomilast, nintedanib or pirfenidone
- Supplemental oxygen: The share of people receiving oxygen therapy is based on FIBRONEER trial data and varies depending on the patients' FVC % predicted and history of acute exacerbation

- Acute exacerbation: A cost of acute exacerbation is applied assuming some people require hospitalisation while some may only attend A&E
- End-of-life costs: A cost is applied upon death to account for palliative care costs

Nerandomilast and nintedanib are subject to confidential price agreements with the NHS, so full cost information cannot be presented. However, nerandomilast is associated with higher treatment acquisition costs than BSC, nintedanib and pirfenidone. This is due to the price of nerandomilast being greater than for pirfenidone and BSC, and due to people on nerandomilast remaining alive for longer and tolerating treatment better – meaning treatment and monitoring costs build up over a longer period of time.

Model results

Overall, the model predicts that treatment with nerandomilast is associated with additional benefit to people (life years and QALYs) alongside additional costs when compared with relevant comparators in both IPF and PPF.

Uncertainty

There are several important sources of uncertainty in both the clinical evidence and the economic modelling:

- There are no trials that directly compare nerandomilast to nintedanib and pirfenidone, so statistical analyses had to be undertaken to compare results across trials (indirect comparisons). However, access to individual patient data from both nerandomilast and nintedanib trials allowed for the most robust statistical methods to be used, limiting uncertainty
- The size of the cohorts with 'no AF background therapy' in the FIBRONEER trials is small. These cohorts inform the rate of FVC decline, mortality, acute exacerbations and number of AEs in the model. With small cohorts, there is more uncertainty around these inputs. Individual parameters were varied to test their impact on the overall results. Despite the small cohort size, the FIBRONEER trials remain the best source of evidence for this analysis
- The FIBRONEER trials have a relatively short follow-up period (1.76 years for FIBRONEER-IPF and 2.12 years for FIBRONEER-ILD). This means that the number of deaths in the trials is low and there is greater uncertainty around what happens to people in the longer-term. Long-term outcomes were validated by clinicians with experience of treating IPF or PPF in England who agreed that nerandomilast would offer a longer-term survival benefit (data on file)
- The number of patients who stopped taking nerandomilast and started next therapy in the FIBRONEER trials is low due to a combination of short trial

follow-ups, small patient numbers, and the fact that a small proportion of patients stopped treatment. This makes it hard to know what treatments patients might get next and how long the benefits of nerandomilast might last after they stop taking it. The duration of effect of taking nerandomilast was varied to test its impact on overall results

- The number of acute exacerbations in the FIBRONEER trials was low, which means these model inputs are uncertain. Additionally, there is inconsistency in how acute exacerbations are defined in practice. For this reason acute exacerbations were assumed not to impact disease progression, although this was tested as an alternative assumption. This allowed us to avoid additional uncertainty being introduced

To help reduce the uncertainties mentioned above, we thoroughly discussed and checked all the information going into and coming out of the model with clinicians (data on file) and extensively tested how changing different assumptions would affect the results.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

As the first preferential inhibitor of PDE4B treatment, nerandomilast offers an innovative new treatment option. Nerandomilast is the first treatment in over a decade to report successful Phase 3 trial completion for people with IPF or PPF.

While the key clinical and safety benefits of nerandomilast (see Section 3h) will be captured in the economic model, there are additional benefits to patients, carers, healthcare services and wider society which are not fully captured. These include:

- Potential improvements in lung function in the short-term. The increase in FVC observed in the FIBRONEER trials over the first 12 weeks of treatment is not captured in the model. This is the first time an improvement in lung function has been observed with PPF treatment where the goal is to slow decline in lung function given the typically irreversible and progressive nature of the disease
- Patient benefits from reduced severe gastrointestinal side effects and improved treatment continuation. While some costs and health benefits of fewer stomach and bowel problems are included in the model, the true burden of these side

effects – including those leading to treatment discontinuation – and the full quality of life gains from reducing them are likely underestimated

- Nerandomilast can be taken with or without food making it easier for people to manage their disease around daily life compared to existing AF medicines which are recommended to only be taken with meals
- Capacity benefits to healthcare services and potential to free up services for other patient groups. While the cost benefits of reduced monitoring, side effect management and supplementary oxygen needs are captured in the model, the benefits associated with time saving and reduced administrative burden are not
- Potential increases in patient contributions to the workforce. Around 20% of people living with IPF and around 60% of people living with PPF report a need for change to working patterns or early retirement due to their disease (data on file) – improved disease control may prevent or at least delay this negative impact
- Potential improvements in carer quality of life. Better control of IPF and PPF can ease the strain on family members or others providing care, helping to protect their health and wellbeing. However, these benefits on carers' quality of life are not captured in the model. Reducing the need for oxygen therapy to help patients breathe is particularly impactful as accessing oxygen can be challenging, increasing patient and carer stress and anxiety[1, 14, 42]
- The general hope and reassurance a new effective treatment option provides to people living with IPF or PPF and their carers, many of whom currently feel underserved by the healthcare system, with some even stating they would prefer a cancer diagnosis because of the better support and care pathways available[1]

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

Regional disparities in access to care may arise due to the limited number of specialist ILD centres. There are only 26 ILD specialist centres in England and Wales, and in some regions, such as the North East of England, a single centre serves all patients. This can make it harder for people with IPF and PPF to attend specialist appointments and maintain regular follow-up.

Long travel distances can be particularly challenging for people who rely on oxygen therapy, as concerns about oxygen supplies running out during journeys may limit their ability or willingness to travel. Travel itself can be physically exhausting, and managing portable oxygen equipment adds further complexity and anxiety. In addition, transport costs and time away from home can be especially difficult for people living in more socio-economically deprived areas, contributing to health inequalities. Socio-economic factors may also limit access to supportive services such as pulmonary rehabilitation, oxygen therapy and palliative care, which are not always fully funded by the NHS.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

FIBRONEER-IPF Plain Language Summary: A Study to Find Out Whether BI 1015550 Improves Lung Function in People With Progressive Fibrosing Interstitial Lung Diseases (PF-ILDs)

FIBRONEER-ILD Plain Language Summary: A Study to Find Out Whether BI 1015550 Improves Lung Function in People With Idiopathic Pulmonary Fibrosis (IPF)

FIBRONEER-IPF Trial Publication: Nerandomilast in Patients with Idiopathic Pulmonary Fibrosis | New England Journal of Medicine

FIBRONEER-ILD Trial Publication: Nerandomilast in Patients with Progressive Pulmonary Fibrosis | New England Journal of Medicine

FIBRONEER-IPF Clinical Trials Record: Study Details | NCT05321069 | A Study to Find Out Whether BI 1015550 Improves Lung Function in People With Idiopathic Pulmonary Fibrosis (IPF) | ClinicalTrials.gov

FIBRONEER-ILD Clinical Trials Record: Study Details | NCT05321082 | A Study to Find Out Whether BI 1015550 Improves Lung Function in People With Progressive Fibrosing Interstitial Lung Diseases (PF-ILDs) | ClinicalTrials.gov

Further information on NICE and the role of patients:

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

4b) Glossary of terms

Acute exacerbation: A sudden worsening of symptoms or lung function in a patient with a chronic lung disease, often triggered by infection, inflammation, or unknown causes. It can lead to rapid deterioration and may require urgent medical treatment.

Clinically meaningful: When a treatment makes a real, noticeable difference to a person's health or quality of life. This could be feeling better, being able to do everyday activities more easily, or having fewer symptoms or side effects.

Cost-effectiveness: Evaluation of the relative costs and benefits of treatment options that help make informed decisions on the best value for money health care options for the NHS.

Delphi panel: A structured process where a group of experts answer questions in several rounds to reach agreement on the best advice or decisions about a topic.

Diarrhoea: Frequent, loose, or watery bowel movements. Can be a symptom of infection, a side effect of medication, or related to other underlying conditions.

Diffusing capacity of the lungs for carbon monoxide: A test that measures how well the lungs move oxygen from the air inhaled into the blood.

Dyspnoea: The medical word for feeling short of breath or having difficulty breathing.

Fatigue: A persistent feeling of tiredness or exhaustion that is not relieved by rest. Common in many chronic illnesses and can markedly impact daily activities.

Fibrosis: The formation of excess fibrous connective tissue in an organ, often as a result of injury or chronic disease. In the lungs, fibrosis causes thickening and scarring, making it harder for oxygen to reach the blood.

Forced vital capacity: The total amount of air a person can blow out after taking the deepest breath possible. Often used to assess lung capacity and disease severity.

High resolution computed tomography: An advanced imaging technique that uses X-rays and computer processing to produce detailed cross-sectional images of the lungs, helping detect and assess lung diseases such as fibrosis.

Interstitial lung disease: A group of disorders that cause progressive scarring (fibrosis) of lung tissue, leading to breathing difficulties and reduced oxygen transfer.

Idiopathic pulmonary fibrosis: A specific type of chronic, progressive interstitial lung disease with unknown cause, characterised by lung tissue scarring and irreversible loss of function.

Monotherapy: Treatment using only a single medicine or therapy, rather than a combination of different ones. In the case of the FIBRONEER trials, nerandomilast or placebo treatment without AF background therapy.

Oxygen therapy: Treatment that provides extra oxygen through a mask or small tubes to help with breathing.

Palliative care: Care that focuses on managing symptoms and supporting quality of life for people living with serious illness such as IPF and PPF.

Phosphodiesterase-4: An enzyme involved in regulating inflammation in the body, particularly the lungs. PDE4 inhibitors are a class of drugs that can reduce inflammation by blocking this enzyme’s activity.

Preferential inhibitor: A medicine that mainly blocks or slows down one specific target in the body (such as an enzyme or pathway) but may still affect others to a smaller degree.

Progressive pulmonary fibrosis: A clinical condition where fibrosis in the lungs worsens over time, regardless of the initial cause, leading to progressive respiratory impairment.

Pulmonary rehabilitation: A supervised programme of exercise, breathing practice, and advice to help people with lung conditions feel better and stay active.

Quality-adjusted life year: A unit used in health economics to measure the value of health outcomes. One QALY equates to 1 year of life in perfect health.

Quality of life: A measure of how healthy, comfortable, and able to enjoy everyday activities a person feels in daily life.

Side effect: An unintended, often adverse, outcome from taking a medication or undergoing a medical intervention. In the FIBRONEER trials, the safety of nerandomilast was measured by recording the number and type of treatment-emergent adverse events (TEAEs), defined as any side effects that started any time from the first dose of the trial medication to 7 days after the last dose.

Standard of care: The best-known treatment or management approach for a particular medical condition, based on evidence, clinical guidelines, and expert consensus.

Usual interstitial pneumonia: A pattern of scarring in the lungs that makes it harder to breathe, often linked to a condition called idiopathic pulmonary fibrosis.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Action for Pulmonary Fibrosis. I wish it was cancer. 2023. Available at: https://cdn.prod.website-files.com/5e32c31d3ab26b41eba332b2/65734c2aa163610a5a3eff7e_MW1307%20ILD%20state%20of%20the%20nation%20report_V8.pdf. Accessed: 26 August 2025.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis [ID6446]

Clarification questions

March, 2026

File name	Version	Contains confidential information	Date
ID6446 Nerandomilast for PF CQs v1.0 31032026 (CON)	1.0	No	31/03/2026

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Identification and selection of relevant evidence

A1. Appendix B.1.4, Pages 29-33. This section of the company submission (CS) refers to the study selection process of the systematic literature reviews (SLRs) for idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF). Please clarify:

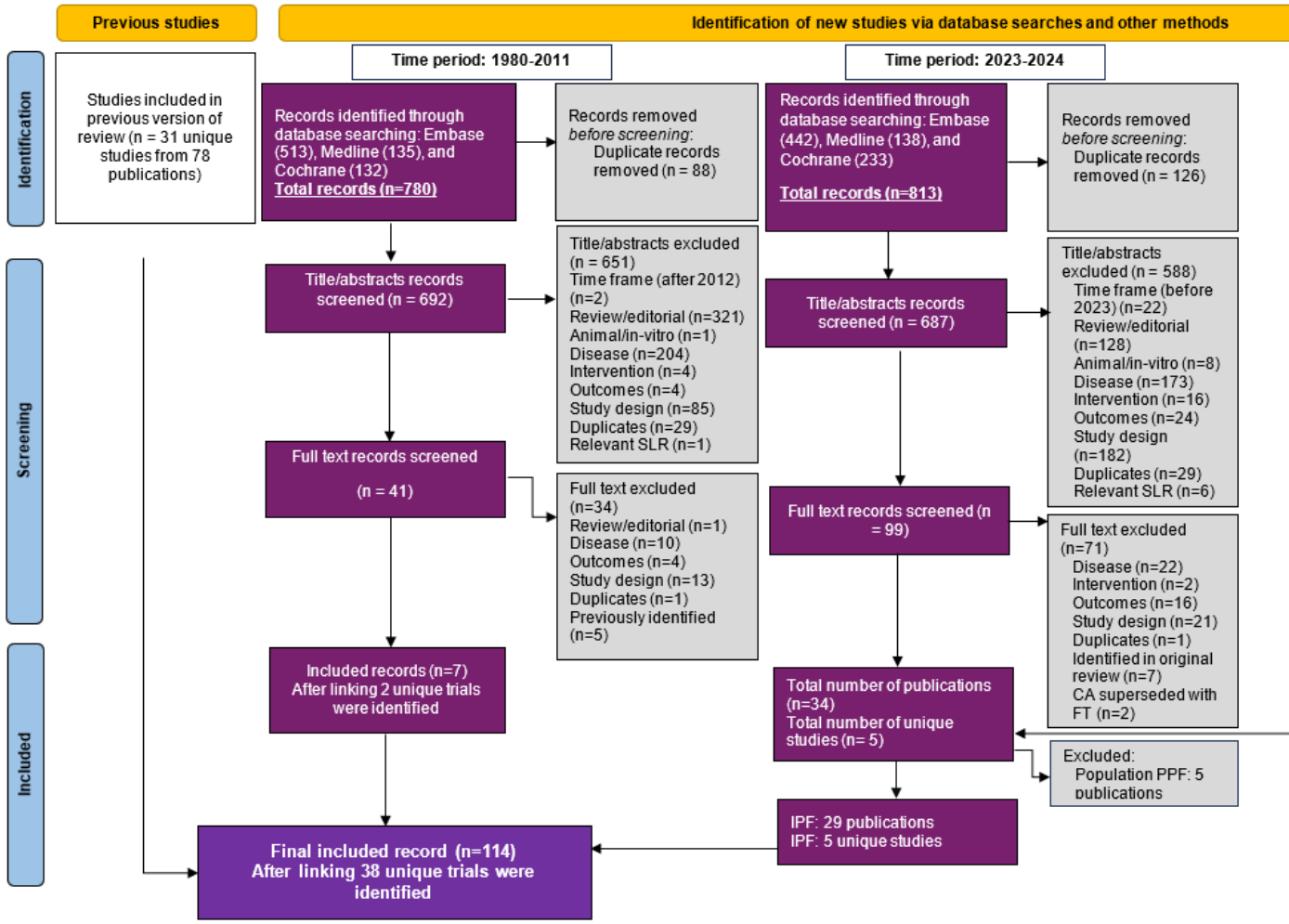
- How many reviewers carried out the title and abstract screening for each review?
- How many reviewers carried out the full text screening for each review?
- Did the reviewers work independently for each review?

Two reviewers carried out the title and abstract screening, and full text screening for each review. The two reviewers worked independently. Any discrepancies between the two reviewer's assessments were resolved by a third independent reviewer.

A2. Appendix B.1.4.3.1, Page 35, Figure 2: PRISMA flow diagram for the 2024 SLR update (IPF). In the PRISMA flow diagram for the 2023–2024 period, the row 2 reports that 588 titles/abstracts were excluded, whereas the individual reasons for exclusion sum to only 582. Please clarify this discrepancy.

Thank you for bringing this to our attention and apologies for the confusion – this was an error in the PRISMA where one category of exclusion (relevant SLR) was not included in the exclusion summary box. A corrected version of Appendix B, Figure 2 is provided below.

Figure 2: PRISMA flow diagram for the 2024 SLR update (IPF)



Key: CA, conference abstract; FT, full text; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; SLR, systematic literature review.

Critical appraisal of the clinical effectiveness evidence

A3. Section 2.5, Pages 56-57 & Appendix B.3, Pages 57-64. Please clarify how many reviewers carried out the risk of bias assessment of the FIBRONEER-IPF and FIBRONEER-ILD studies and whether the reviewers worked independently.

The risk of bias assessment of the FIBRONEER-IPF and FIBRONEER-ILD studies was conducted by one reviewer and verified against the original source(s) by a second reviewer. Any discrepancies in the two reviewer assessments were referred to a third independent reviewer for resolution.

Methodology for clinical effectiveness evidence

A4. Section 2.3.2, Table 5, Page 51. Table 5 (Baseline characteristics of patients, FIBRONEER-IPF “no AF background therapy” cohort) reports Nera 18 mg bid (n = 87), Nera 9 mg bid (n = 88), and placebo (n = 87); however, the total sample size is given as N = 172. Please clarify this apparent discrepancy in participant numbers.

Thank you for bringing this to our attention and apologies for the confusion – this was a typographical error. A corrected version of Table 5 is provided below and in the corrected company submission document re-submitted alongside clarification questions responses.

Table 5: Baseline characteristics of patients, FIBRONEER-IPF ('no AF background therapy' cohort)

Characteristic	Nera 18 mg bid N = 87	Nera 9 mg bid N = 88	Placebo N = 87	Total N = 262
Male sex, n (%)	68 (78.2)	63 (71.6)	68 (78.2)	199 (76.0)
Age, mean (SD), years	70.1 (8.8)	70.3 (8.4)	70.9 (8.2)	70.4 (8.4)
Weight, mean (SD), kg	71.86 (13.4)	73.41 (16.4)	74.4 (14.2)	73.23 (14.7)
Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Black/African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Multiple, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)[a]				
Never smoked	29 (33.3)	25 (28.4)	23 (26.4)	77 (29.4)
Former smoker	56 (64.4)	60 (68.2)	61 (70.1)	177 (67.6)
Current smoker	2 (2.3)	3 (3.4)	3 (3.4)	8 (3.1)
Time since diagnosis of IPF, mean (SD), years	2.93 (3.1)	2.78 (2.5)	2.78 (3.2)	2.83 (2.9)
FVC				
Mean value (SD), mL	2761.4 (778.4)	2763.6 (739.3)	2833.3 (885.7)	2786 (800.9)
Mean % predicted (SD)	82.1 (18.7)	82.31 (15.7)	82.18 (19.5)	82.2 (17.9)
DL_{CO}, mean % predicted (SD)[b]	57.1 (18.4)	57.38 (18.5)	51.03 (17.5)	55.18 (18.3)
Previous AF use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
AF naïve, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Supplemental oxygen therapy, n (%)	14 (16.1)	11 (12.5)	17 (19.5)	42 (16.0)

Key: AF, antifibrotic; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; nera, nerandomilast; SD, standard deviation.
Notes: [a] Percentages may not total 100 because of rounding. [b] Values corrected for haemoglobin level.
Source: FIBRONEER-IPF CTR (Tables 15.1.7.6: 2–15.1.7.6: 4)[1]; Richeldi et al. 2025.[2]

A5. Section 2.3.2 (patient baseline characteristics), Page 50. Regarding the FIBRONEER trial population, the CS states that, compared with the "typical UK patient," the FIBRONEER-ILD population had different underlying ILD diagnoses, a higher proportion of 'UIP-like' fibrotic patterns, and a higher proportion of males. In contrast, the FIBRONEER-IPF population was slightly younger, had fewer comorbidities, and had a longer disease duration. Please clarify how the "typical UK patient" is defined and the basis for this comparison**.**

The 'typical UK patient' refers to a patient profile that reflects the average demographics and clinical characteristics of individuals referred to UK interstitial lung disease (ILD) services. The basis of this reference and subsequent conclusions was derived by qualitative clinical insights gathered through a UK advisory board convened to discuss the FIBRONEER trials.[3] This advisory board panel included key UK clinical stakeholders – respiratory physicians, rheumatologists, ILD specialist nurses, and pharmacists – who manage ILD patients routinely in day-to-day practice.

The advisory board panel were presented with the baseline characteristics of the FIBRONEER-ILD and FIBRONEER-IPF populations and asked to comment on their comparability to real-world practice patients. The overall conclusions were as summarised in the company submission (CS). For a complete overview of the full discussion, please refer to the clinical advisory board report provided in the reference pack.[3] When discussing the fibrotic patterns of patients enrolled in the FIBRONEER-ILD trial, the advisory board panel noted a high proportion of 'UIP-like' fibrotic patterns, not a higher proportion as suggested in this question. This high proportion of 'UIP-like' fibrotic patterns is not unexpected as the trial is selecting a progressive cohort of ILD patients. With regard to the underlying ILD diagnoses of patients, some members of the advisory board panel felt the proportional split of underlying diagnoses differed to their individual clinical practice but the underlying ILD diagnoses included were representative of the PPF real-world population. Of note, the comorbidities comment on the FIBRONEER-IPF was an assumption of the advisory board panel based on their general experience of trial populations having fewer comorbidities than real-world patient populations.

To further assess the characteristics of patients diagnosed with IPF and PPF, as well as their diagnosis pathways, treatment patterns, healthcare resource use and clinical

outcomes, we sponsored a real-world evidence (RWE) study. The Treatments and Real-world Insights in Patients with Pulmonary fibrosis (TRIPP) study retrospectively collected data on adult patients diagnosed with IPF between 1 January 2014 and 31 December 2023 or PPF between 1 January 2021 and 31 December 2023 at University Hospitals Birmingham NHS Foundation Trust (UHB) – one of the ILD specialist centres in the UK.[4]

A comparison of the baseline characteristics of patients in the FIBRONEER trials and the TRIPP study is provided in Table 1.

Table 1: Baseline characteristics of patients, FIBRONEER trials ('no AF background therapy' cohort) and TRIPP study

Characteristic	FIB-IPF N = 262	TRIPP-IPF N = 942	FIB-ILD N = 662	TRIPP-PPF N = 245
Male sex, n (%)	199 (76.0)	[redacted]	330 (49.8)	[redacted]
Age, mean (SD), years	70.4 (8.4)	[redacted]	66.2 (10.4)	[redacted]
Smoking status, n (%)[a]		[redacted]		[redacted]
Never smoked	77 (29.4)	[redacted]	364 (55.0)	[redacted]
Former smoker	177 (67.6)	[redacted]	280 (42.3)	[redacted]
Current smoker	8 (3.1)	[redacted]	18 (2.7)	[redacted]
Time since diagnosis of ILD, mean (SD), years	2.83 (2.9)	[redacted]	4.0 (4.1)	[redacted]
FVC		[redacted]		[redacted]
Mean value (SD), mL	2,786 (801)	[redacted]	2,287 (738)	[redacted]
Mean % predicted (SD)	82.2 (17.9)	[redacted]	71.1 (16.0)	[redacted]
DL_{CO}, mean % predicted (SD)[b]	55.18 (18.3)	[redacted]	52.5 (16.7)	[redacted]
Previous AF use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
AF naïve, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Supplemental oxygen, n (%)	42 (16.0)	-	127 (19.2)	-
Underlying ILD diagnoses, n (%)				
Autoimmune ILDs	-	-	214 (32.3)	[redacted]
Hypersensitivity pneumonitis	-	-	111 (16.8)	[redacted]
Unclassifiable idiopathic interstitial pneumonia	-	-	120 (18.1)	
Idiopathic non-specific interstitial pneumonia	-	-	137 (20.7)	
Other ILDs	-	-	80 (12.1)	

Characteristic	FIB-IPF N = 262	TRIPP-IPF N = 942	FIB-ILD N = 662	TRIPP-PPF N = 245
Baseline UIP or UIP-like fibrotic pattern	-	-	474 (71.6)	-
Other fibrotic pattern	-	-	188 (28.4)	-

Key: AF, antifibrotic; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; nera, nerandomilast; SARD, Systemic Autoimmune Rheumatic Disease; SD, standard deviation.
Notes: [a] Percentages may not total 100 because of rounding; [b] Values corrected for haemoglobin level; [c] SARD-ILDs.
Source: FIBRONEER-ILD CTR (Tables 15.1.7.6: 2–15.1.7.6: 4)[5]; FIBRONEER-IPF CTR (Tables 15.1.7.6: 2–15.1.7.6: 4)[1]; Maher et al. 2025.[6]; Richeldi et al. 2025.[2]; TRIPP study report.[4]

The characteristics highlighted by the advisory board panel are difficult to compare due to differences in data reporting, but the RWE data are not fully supportive of the clinical experts' opinions. For example, the proportion of males in the PPF cohort of the TRIPP study was higher than in FIBRONEER-ILD. There are obvious limitations in such naïve comparisons, and the TRIPP study representing a single centre cohort of patients at the point of diagnosis, but these data do further show the heterogeneity of the pulmonary fibrosis patient population, particularly those with PPF as discussed in the CS. Importantly, nerandomilast was shown to be effective across patient subgroups in the FIBRONEER trials, with no significant difference in FVC outcomes due to sex, age, underlying ILD diagnoses or fibrotic patterns (see CS Appendix C).

A6. Section 2.5, Page 57 & Section 2.13.2, Page 127. The CS refers to the rules for concomitant immunosuppressant medication used in the FIBRONEER-ILD trial. Please provide more details on these rules. If available, please also include the proportion of trial participants who received concomitant immunosuppressants, the types of immunosuppressant therapy used, and any implications this may have had on the characteristics of the trial population.

In FIBRONEER-ILD, the following immunosuppressive agents were not permitted prior to study, during screening or during the treatment period: prednisone > 15 mg/day or equivalent, cyclophosphamide, tocilizumab, rituximab, mycophenolate with the following exceptions:

- Prednisone > 15 mg/day or equivalent could be prescribed during the treatment period in case of (suspected) acute ILD exacerbation

- After 6 months from randomisation, changes in immunomodulatory treatment were allowed to manage any worsening of the underlying disease as medically indicated

Patients treated with permitted immunosuppressive agents (other than corticosteroids) for an underlying systemic disease (e.g. methotrexate, azathioprine, hydroxychloroquine) needed to be on a stable treatment for at least 12 weeks before the screening visit (Visit 1) and during the screening period. Addition or changes in immunomodulatory treatment (except of dose adjustments of prednisone up to 15 mg, which were allowed) were not to occur during the first 6 months of blinded treatment.

In the FAS a total of 283 (24.1%) patients used immunosuppressive medications at baseline (see Table 10: 15 of the clinical trial report [CTR] for a breakdown of baseline immunosuppressant use in the FAS). A total of 97 (8.2%) patients initiated immunosuppressive therapy during the on-treatment period up to database lock 1 (DBL1) (see Table 10: 16 of the CTR for a breakdown of on-treatment immunosuppressant use in the FAS). No relevant differences between treatment groups were observed in the initiation of immunosuppressive therapy during the study period.

In the monotherapy population ('no AF background therapy' cohort) a total of 195 (29.5%) patients used immunosuppressive medications at baseline, as summarised in Table 2. A total of 67 (10.1%) patients initiated immunosuppressive therapy during the on-treatment period up to database lock 2 (DBL2), as summarised in Table 3.

Table 2: Baseline immunosuppressant use (frequency >1% in any treatment group), FIBRONEER-ILD ('no AF background therapy' cohort)

	Nerandomilast 18 mg bid N=220	Nerandomilast 9 mg bid N=220	Placebo N=222	Total N=662
≥1 baseline immunosuppressant of interest	[redacted]	[redacted]	[redacted]	[redacted]
Azathioprine	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]

	Nerandomilast 18 mg bid N=220	Nerandomilast 9 mg bid N=220	Placebo N=222	Total N=662
Hydroxychloroquine Sulphate	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxychloroquine	[redacted]	[redacted]	[redacted]	[redacted]
Tacrolimus	[redacted]	[redacted]	[redacted]	[redacted]
Ciclosporin	[redacted]	[redacted]	[redacted]	[redacted]
Leflunomide	[redacted]	[redacted]	[redacted]	[redacted]
Abatacept	[redacted]	[redacted]	[redacted]	[redacted]
Colchicine	[redacted]	[redacted]	[redacted]	[redacted]
Iguratimod	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate Sodium	[redacted]	[redacted]	[redacted]	[redacted]
Source: FIBRONEER-ILD CSAP (Table 69.1.3.3.3).[7]				

Table 3: On-treatment immunosuppressant use (frequency >1% in any treatment group), FIBRONEER-ILD ('no AF background therapy' cohort)

	Nerandomilast 18 mg bid N=220	Nerandomilast 9 mg bid N=220	Placebo N=222	Total N=662
≥1 baseline immunosuppressant of interest	[redacted]	[redacted]	[redacted]	[redacted]
Mycophenolate Mofetil	[redacted]	[redacted]	[redacted]	[redacted]
Azathioprine	[redacted]	[redacted]	[redacted]	[redacted]
Tacrolimus	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxychloroquine Sulphate	[redacted]	[redacted]	[redacted]	[redacted]
Tacrolimus Monohydrate	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]	[redacted]
Pirfenidone	[redacted]	[redacted]	[redacted]	[redacted]
Source: FIBRONEER-ILD CSAP (Table 69.1.3.3.4).[7]				

As acknowledged in the CS (Section 2.13), there was an applicability concern raised in relation to concomitant immunosuppressant medication rules applied in the FIBRONEER-ILD trial, with clinical experts noting mycophenolate and rituximab are two of the most common immunosuppressants used to manage PPF in UK clinical practice. Patients receiving these treatments were excluded from the FIBRONEER-ILD trial to avoid any potential confounding impact of these drugs on the assessment of the efficacy and safety of nerandomilast.[5] The suggestion was that this could have impacted the severity of disease profile of patient, that is, by selecting only those patients not receiving such immunosuppressive agents you are selecting the patients whose disease is not severe enough to need such active management.

The disease characteristics of patients enrolled to FIBRONEER-ILD show this was not the case, with the FVC % predicted and DLco % predicted values at baseline similar to the real-world patient population of the TRIPP study, the PPF-ILD Disease Specific Programme (DSP) in the UK and previous PPF trial populations (Table 4). Clinical experts speculated that some patients may have been entered into the trial instead of starting mycophenolate or rituximab treatment. Nonetheless, they all still agreed that the FIBRONEER-ILD population broadly reflects the PPF population they treat in clinical practice and the heterogeneity within this patient population.

Table 4: Baseline characteristics of patients, FIBRONEER-ILD ('no AF background therapy' cohort), INBUILD and real-world studies (TRIPP-PPF and Adelphi-PPF DSP)

Characteristic	FIB-ILD N = 662	INBUILD N = 663	TRIPP-PPF N = 245	Adelphi-PPF DSP N = 208
Male sex, n (%)	330 (49.8)	356 (53.7)	[redacted]	[redacted]
Age, mean (SD), years	66.2 (10.4)	65.8 (9.8)	[redacted]	[redacted]
Smoking status, n (%)[a]			[redacted]	[redacted]
Never smoked	364 (55.0)	325 (49.0)	[redacted]	[redacted]
Former smoker	280 (42.3)	327 (49.3)	[redacted]	[redacted]
Current smoker	18 (2.7)	11 (1.7)	[redacted]	[redacted]
Time since diagnosis of ILD, mean (SD), years	4.0 (4.1)	≥6 months, n (%): 588 (88.7)	[redacted]	[redacted]
FVC			[redacted]	[redacted]
Mean value (SD), mL	2,287 (738)	2,331 (734)	[redacted]	[redacted]
Mean % predicted (SD)	71.1 (16.0)	69.0 (15.6)	[redacted]	[redacted]
DL_{CO}, mean % predicted (SD)[c]	52.5 (16.7)	46.1 (13.6)	[redacted]	[redacted]
Previous AF use, n (%)	[redacted]	-	[redacted]	[redacted]
AF naïve, n (%)	[redacted]	-	[redacted]	[redacted]

Characteristic	FIB-ILD N = 662	INBUILD N = 663	TRIPP-PPF N = 245	Adelphi-PPF DSP N = 208
Use of immunosuppressants[d], n (%) Mycophenolate, n (%) Rituximab, n (%)	[redacted]	7 (1.1) 3 (<1) 1 (<1)	[redacted]	[redacted]
Supplemental oxygen, n (%)	127 (19.2)	134 (20.2)	-	-
Underlying ILD diagnoses, n (%)				
Autoimmune ILDs	214 (32.3)	170 (25.6)	[redacted]	[redacted]
Hypersensitivity pneumonitis	111 (16.8)	173 (26.1)	[redacted]	[redacted]
Unclassifiable idiopathic interstitial pneumonia	120 (18.1)	114 (17.2)		
Idiopathic non-specific interstitial pneumonia	137 (20.7)	125 (18.9)		
Other ILDs	80 (12.1)	81 (12.2)		
Baseline UIP or UIP-like fibrotic pattern	474 (71.6)	412 (62.1)	-	-
Other fibrotic pattern	188 (28.4)	251 (37.9)	-	-

Key: AF, antifibrotic; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; DSP, disease specific programme; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; nera, nerandomilast; SARD, Systemic Autoimmune Rheumatic Disease; SD, standard deviation.
Notes: [a] Percentages may not total 100 because of rounding; [b] Most recent data to survey date (within 12 months); [c] Values corrected for haemoglobin level. [d] at baseline or any time post-baseline; [e] SARD-ILDs.

Source: FIBRONEER-ILD CTR (Tables 15.1.7.6: 2–15.1.7.6: 4)[5]; CSAP – 228 (Table 69.1.3.3.3) ; Flaherty et al. 2019[8]; Maher et al. 2025.[6]; TRIPP study report[4]; Adelphi-PPF DSP supplementary data file[9].

Adverse events

A7. Section 2.11, Pages 106-122, Tables 20, 21, 25 & 26. These tables report on "Severe AEs (CTCAE Grade ≥3)" and/or "Serious AEs." Please define each term and clarify how they differ.

In the FIBRONEER studies, 'Severe AEs (CTCAE Grade ≥3)' and 'Serious AEs' describe different concepts. Severe AEs are defined by the Common Terminology Criteria for Adverse Events (CTCAE) grading system and refer to the clinical intensity of an adverse event. In this case a 'Severe AE' refers to a severe or medically significant but not immediately life-threatening AE.[1, 5] This classification focuses on how intense the symptoms are. In contrast, 'Serious AEs' refer to events that have major clinical consequences, such as resulting in death, being life-threatening, requiring inpatient hospitalisation or prolongation of hospitalisation, resulting in persistent or significant disability or incapacity, and/or requiring medical or surgical intervention to prevent death, disability or hospitalisation.[1, 5] An AE can be severe without being serious (for example, severe symptoms treated in an outpatient setting), and it can be serious without being severe (for example, a mild event that leads to hospitalisation). Thus, severity describes how bad the event is, while seriousness describes the outcome of the event.

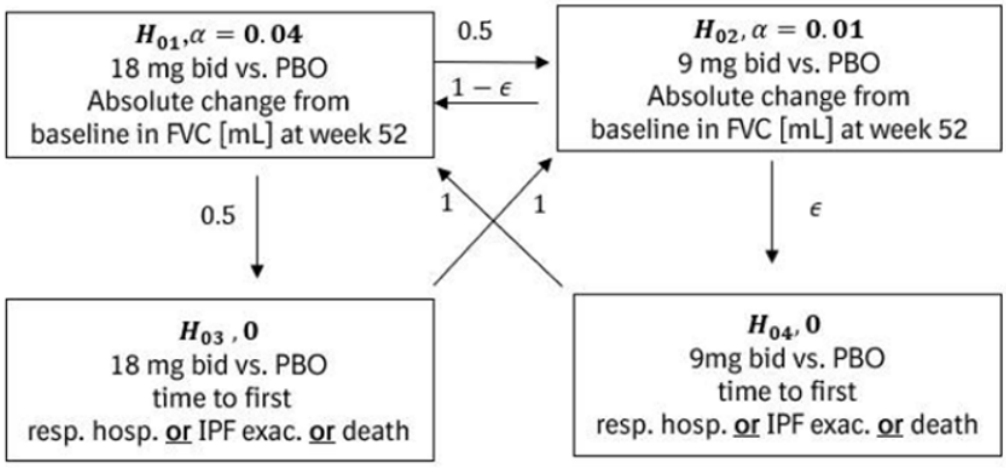
Statistical analysis in the relevant clinical effectiveness evidence

A8. Section 2.4, Page 53. The CS states that multiplicity-adjusted analyses were conducted for the primary and key secondary outcomes. Please report results using 97.5% confidence intervals for all analyses that applied a multiplicity adjustment.

We acknowledge that in the original report the multiplicity adjustment and alpha control employed in the FIBRONEER trials was not clearly defined and hence would like to clarify further. In the clinical trial, multiplicity adjustment and alpha control was adjusted through hierarchical testing of primary and key secondary endpoint (KSE) for both 18 mg and 9 mg doses, and not through simultaneous testing.[10] To be specific, at the first step of testing (for the primary endpoint), alpha was split between the two primary endpoint comparisons as follows – 0.04 assigned to 18 mg primary endpoint test, remaining 0.01 assigned to 9 mg primary endpoint test. Once the primary endpoint for the leading dose (18 mg) was significant, the alpha was further

split and assigned to the primary endpoint for 9 mg and KSE for 18 mg (please see Figure 1). As this testing procedure abides to the closed test principle, it holds strong control of family-wise Type 1 error rate at two-sided alpha level of 0.05.

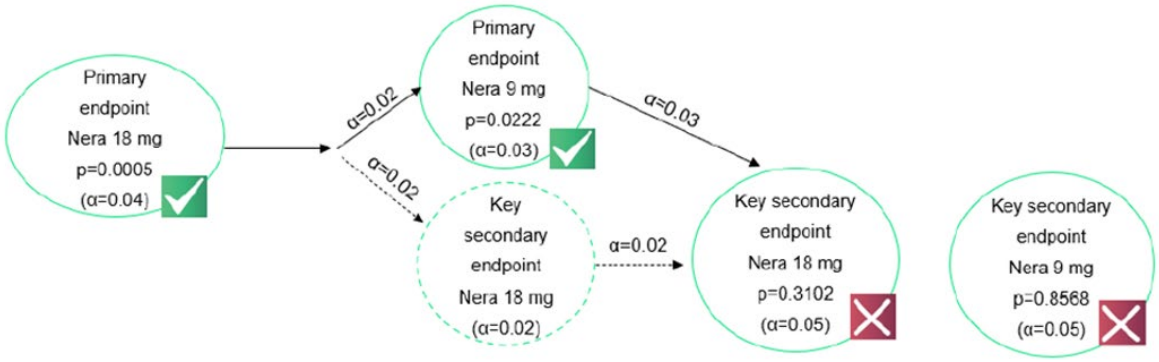
Figure 1. Graphical testing procedure for hypothesis testing strategy



Key: bid, twice-daily; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; PBO, placebo

To explain this sequential testing further, please see Figure 2 which explains how alpha was split across the primary and KSE outcomes in the IPF trial.

Figure 2. Confirmatory testing results



Key: Nera, nerandomilast

A9. Section 2.4, Table 7, Page 55. The key secondary endpoint was time to first occurrence of any of the components of the composite endpoint: time to first acute

IPF (in FIBRONEER-IPF) or ILD (in FIBRONEER-ILD) exacerbation, first hospitalisation for respiratory cause, or death. Please:

- Provide further justification for the decision to use a Cox proportional hazards model, instead of a competing risks model for this composite endpoint.
- Consider providing results of a competing risks model.

In the FIBRONEER trials, the Cox proportional hazards model was prespecified for time to event endpoints, including the key secondary endpoint (KSE) and death. Because these endpoints include death as part of the composite, competing risk methods were not considered necessary.

Additional clinical outcome endpoints, such as time to first acute exacerbation, that do not include death were considered as further endpoints in the protocol. For these outcomes, death may act as a competing event because it prevents the occurrence of subsequent events of interest. Non-terminal events such as acute exacerbation and hospitalisation were not considered competing risks because the occurrence of one does not preclude the other.

A cause-specific competing risk model was prespecified for these further endpoints, consistent with commonly used approaches in the literature[11-13] and by regulatory agencies.[14] Under this method, patients are censored at death and removed from the risk set for non-fatal events. Although the Fine–Gray subdistribution model[15] is an alternative for estimating treatment effects on cumulative incidence, it has been criticized for statistical and interpretability issues, including potential event probabilities exceeding 1 and challenges in causal interpretation.[16-19] Conceptually, retaining patients in the risk set after death assumes they remain event free, which can attenuate the estimated effect of treatments that reduce mortality.

Therefore, based on the rationale provided above, a prespecified cause-specific competing-risk model, i.e. the Cox proportional hazards model with death censored is a more appropriate statistical approach compared to a competing risk model.

A10. Section 2.4, Page 53. The company submission states that “The primary endpoint was analysed with the use of a mixed-effects model for repeated measures, with the following covariates: treatment at each visit, baseline AF background

therapy (yes/no), continuous fixed effects for baseline FVC (mL) at each visit and HRCT pattern (UIP-like fibrotic pattern versus other fibrotic patterns) – FIBRONEER-ILD only." Please clarify the random-effects structure specified in the repeated measures mixed-effects models.

Visit was treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements. For full details of the statistical model, please see Section 7.4 of the Trial Statistical Analysis Plan for FIBRONEER-ILD provided in the reference pack.[10]

Section B: Clarification on cost-effectiveness data

Economic model structure

B1. <u>PRIORITY.</u> Section 3.2.2, Figure 34, Page 132. This figure shows potential for improvement in FVC over time; however, the description in the text describes a condition that can only progress in severity over time. Please provide any available data to demonstrate what, if any, potential exists for improvement in FVC over time, detailing how this is likely to differ across treatment arms of the model**.**

In the FIBRONEER trials, a subset of patients randomised to nerandomilast showed an initial improvement in FVC in the early weeks of treatment. This can be seen in Figures 9 and 11 of the CS. The initial improvement in FVC is only observed for patients randomised to nerandomilast, for whom the subsequent FVC values are consistently higher than for patients randomised to placebo.

Figure 34 in the CS, depicting the economic model structure, demonstrates that patients can only progress in severity over time, in line with the written description provided. This is reflected through the Poisson regression approach, which estimates a constant rate of 'FVC decline events' defined as each 10% loss in FVC % predicted from baseline. A limitation of this approach is that improvements above baseline observed in FIBRONEER trials are not directly captured within this analysis – therefore providing a conservative estimate on the efficacy of nerandomilast.

At the previously described advisory board panel (see response to A5) the initial improvement in FVC observed with nerandomilast treatment was a key point of interest to UK clinical stakeholders.[3] The improvements in FVC seen as early as

Week 2 was highlighted as unprecedented and reinforces the concept of a dual mechanism of nerandomilast with the initial improvement suggestive of an anti-inflammatory effect.[3]

Evidence from key comparator trials (INPULSIS/INBUILD/CAPACITY) supports the advisory board discussion, largely demonstrating slowing of FVC decline rather than population-level improvement above baseline.[20-22] As the increase in FVC observed for nerandomilast is not explicitly modelled, as noted in the CS (Section 3.13), the cost-effectiveness of nerandomilast is likely to be underestimated.

B2. <u>PRIORITY.</u> Section 3.2.2, Figure 34, Page 132.

The economic model structure does not consider lung transplantation as a treatment option of health state for advanced disease. Please:

- Provide full details of the numbers and percentages of participants across all considered studies who received a lung transplant in the trials.
- Provide further justification as to why the exclusion of lung transplantation does not bias results. If there are likely to be any biases, please comment on the direction of those biases and provide a clinical justification to support the response.
- If possible, please provide a scenario analysis exploring the impact of including lung transplantation in the economic model.

As noted in the CS, a small proportion of patients with IPF or PPF ultimately undergo lung transplantation; this is borne out in the FIBRONEER trial programme, real-world evidence and clinician estimates.

Further details of the FIBRONEER trial participants that had a lung transplant are provided in Table 5. While patient numbers are too small to make any meaningful conclusions based on these data, there are no signals of difference in the rate of lung transplant across treatment arms.

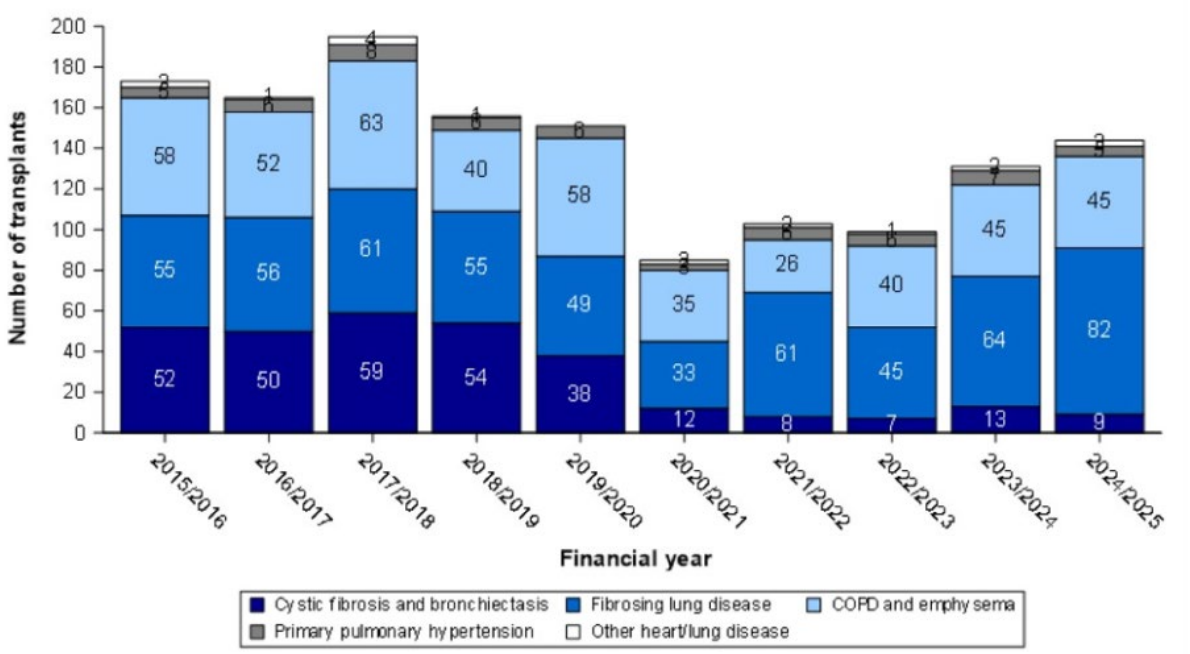
Table 5: Percentage of trial participants that had a lung transplant out of those that completed planned observation, had lung transplant or died up to DBL2

	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo	Total
FIBRONEER-IPF				
Lung transplant in FAS, n (%)	6 (1.5)	7 (1.8)	9 (2.3)	22 (1.9)
Lung transplant in monotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
FIBRONEER-ILD				
Lung transplant in FAS, n (%)	10 (2.6)	3 (0.8)	10 (2.6)	23 (2.0)
Lung transplant in monotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: bid, twice a day; FAS, final analysis set; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.
Sources: FIBRONEER-IPF CTR (Table 10.4)[1]; CSAP-137 (Table 47.1.1.1)[23]; FIBRONEER-ILD CTR (Table 10.5)[5]; CSAP-228 (Table 69.1.1.1).[7]

To further demonstrate the low numbers of lung transplants for pulmonary fibrosis in the UK, we looked to the NHS annual report on lung transplantation, which confirmed there were only 82 lung transplants for fibrosing lung disease between 1 April 2024–31 March 2025, as shown in Figure 3. Similarly, in the TRIPP study fewer than [redacted] lung transplants were reported in both the IPF [redacted]) and PPF [redacted] cohorts.[4] As part of the structured expert elicitation undertaken to provide evidence for mortality estimates in the CEM, one clinician estimated that only 1–2% of patients could be expected to undergo transplantation.[24]

Figure 3: Number of adult lung only transplants in the UK, by financial year and disease group, 1 April 2015 to 31 March 2025



Key: COPD, chronic obstructive pulmonary disease.
Source: NHS Blood and Transplant 2025.[25]

A robust scenario analysis that explicitly models lung transplantation is not feasible with the current evidence. It would require treatment arm-specific transplant rates over time plus credible post-transplant survival, costs, and utilities, which are not reliably captured in the FIBRONEER trials due to very low event counts. Transplant is also a competing event and likely associated with informative censoring, so the current survival extrapolations do not reflect the post-transplant shift in risk, costs, or quality of life. As a result, adding an explicit transplant pathway would be driven largely by strong, untestable assumptions and could give a false sense of precision.

The exclusion of lung transplantation does not bias results because so few events of this nature occur in real-world practice or in the clinical trial setting. Although transplantation is likely to increase costs and may extend survival, the net QALY impact is uncertain because post-transplant quality of life may still be driven by overall disease progression and transplant-related morbidity. If there were any biases, they would be of unknown direction. Hence, we cannot quantify the net post-transplant impact on life years, QALYs, and costs, and there is no robust evidence to suggest transplants occur more frequently or earlier in one treatment arm than the other. We also do not know how post-transplant outcomes differ from the model's

extrapolated natural history, which reinforces that we cannot determine whether including transplantation would increase or decrease incremental costs and QALYs. In light of these limitations, we do not feel this is an appropriate scenario to incorporate into the economic modelling and overall is not relevant to the decision problem for this appraisal.

Modelled population

B3. PRIORITY. Section 3.2.1, Page 131. Please confirm how the 'No AF Background Therapy' cohort is derived. Specifically, does this refer to a subpopulation who were receiving dual therapy after baseline in the clinical trials, or to participants who were antifibrotic (AF) therapy-naïve at study entry? Please also comment on the generalisability of this cohort to the population most likely to receive nerandomilast in UK clinical practice.

The 'no AF background therapy' cohort was defined based on concomitant treatment during the trial and includes participants who were not receiving background nintedanib or pirfenidone in-study.[1, 5] Randomisation in both trials was stratified by the presence of AF background therapy (yes versus no). The 'no AF background therapy' cohort represents the intended use of nerandomilast as a monotherapy rather than an add-on treatment to AF therapy / dual therapy in clinical practice.

This cohort should not be interpreted as participants who were AF therapy-naïve at study entry. The 'no AF background therapy' cohort includes both AF therapy-naïve patients and patients with prior AF use who met the required washout period (i.e., not on nintedanib/pirfenidone for at least 8 weeks before Visit 1 and during screening).[1, 5] As shown in Table 6, the majority of patients in the 'no AF background therapy' cohort of both FIBRONEER trials were AF therapy-naïve at study entry.

Table 6: Antifibrotic treatment history in the 'no AF background therapy' cohorts of the FIBRONEER trials

	Nera 18 mg bid	Nera 9 mg bid	Placebo	Total
FIBRONEER-IPF				
N	87	88	87	262
Previous AF use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

	Nera 18 mg bid	Nera 9 mg bid	Placebo	Total
AF naïve, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
FIBRONEER-ILD				
N	220	220	222	662
Previous AF use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
AF naïve, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Sources: FIBRONEER-IPF CTR (Table 15.1.7.6:5)[1]; FIBRONEER-ILD CTR (Table 15.1.7.6:5)[5];				

Pooled analyses of FIBRONEER-IPF and FIBRONEER-ILD show no clinically meaningful or significant differences in the treatment effect of nerandomilast 18 mg bid in patients based on AF treatment history, as shown in Figure 4 and Figure 5. This supports the proposed positioning of nerandomilast within the current care pathway, as described in the CS Section 1.3.4.3. In brief, this is as a treatment option for newly diagnosed / AF treatment naïve patients as well as patients who have previously received and failed AF treatment (see CS Figure 5 and Figure 6).

Figure 4: Adjusted mean change from baseline in FVC (mL) up to DBL2 based on history of AF treatment, FIBRONEER-IPF and FIBRONEER-ILD pooled



Key: AF, antifibrotic; bid, twice a day; CI, confidence interval; DBL2, database lock 2; FVC, forced vital capacity; Nera, nerandomilast.
Source: FIBRONEER-IPF and -ILD pooled analyses – Supplementary CSAP.[26]

Figure 5: Time to first acute exacerbation, first hospitalisation for respiratory cause or death up to DBL2 based on history of AF treatment, FIBRONEER-IPF and FIBRONEER-ILD pooled



Key: AF, antifibrotic; bid, twice a day; CI, confidence interval; DBL2, database lock 2; Nera, nerandomilast.
Source: FIBRONEER-IPF and -ILD pooled analyses – Supplementary CSAP.[26]

With regard to generalisability, insights from the UK advisory board support the use of nerandomilast as monotherapy rather than as an add-on treatment to AF therapy / dual therapy in clinical practice.[3] Therefore the 'No AF background therapy' is more reflective of the population intended to receive nerandomilast in UK clinical practice, than the full population of the FIBRONEER trials.

At the clarification question (CQ) discussion meeting, the EAG also asked about subsequent treatment use in the FIBRONEER trials. Please refer back to the CS Section 2.7 for data on subsequent treatment; in the nerandomilast 18 mg bid monotherapy cohorts, [redacted] patients in FIBRONEER-IPF received subsequent AF treatment and [redacted] of patients in FIBRONEER-ILD received subsequent AF treatment. No meaningful conclusions could be made from further exploration of these patients.

Clinical parameters in the economic model

B4. <u>PRIORITY.</u> Section 3.3.4, Pages 163-165 (risk of acute exacerbations).

Using the pooled trial data, please provide a cross tabulation of the risk of acute exacerbations for each FVC health state from the economic model. The results of

model predictions are provided in Table 44. However, please also report the summary data, reported as a cross tabulation of n/N (%).

As requested, the number of acute exacerbation events by FVC % predicted health states (Table 7) and by treatment and FVC % predicted health states (Table 8 for IPF, Table 9 for PPF, Table 10 for pooled IPF and PPF) are presented below. In these tables, 'records' refer to the number of individual patient follow-ups where patients current FVC % predicted was falling within a specific FVC % predicted category. 'Patients' is the number of individual patients with at least one of these follow-ups. 'Events' is the number of acute exacerbation events during the whole trial follow-up for patients with current FVC % predicted in a given category at the time of the event.

As an example, looking at the first set of rows (i.e. FVC % predicted [-Inf, 40)) and columns (i.e. FIBRONEER-IPF and INPULSIS), the interpretation should be that [redacted] acute exacerbation were observed out of [redacted] patients over [redacted] visits, during which their current FVC % predicted was <40% (Table 7). Please note that patients can be counted in more than one FVC % predicted category, as their FVC % predicted declines over the trial follow-up.

Overall the results across trials and indications are broadly similar; however, due to the low event counts by FVC % predicted health states, it is challenging to drawing any definitive conclusions.

Table 7. Observed Acute Exacerbations by FVC % Predicted Health States

FVC % predicted	FIBRONEER-IPF DBL2 and INPULSIS Final DBL Pooled Trial Data				FIBRONEER-ILD DBL2 and INBUILD Final DBL Pooled Trial Data				FIBRONEER-ILD DBL2, FIBRONEER-IPF DBL2, INPULSIS Final DBL and INBUILD Final DBL Pooled Trial Data			
	records	patients	events	records/events	records	patients	events	records/events	records	patients	events	records/events
[-Inf,40)	[redacted]											
[40,50)	[redacted]											
[50,60)	[redacted]											
[60,70)	[redacted]											
[70,80)	[redacted]											
[80,90)	[redacted]											
[90, Inf)	[redacted]											

Key: bid, twice a day; DBL, database lock; FVC(pp), forced vital capacity (% predicted); ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.
Source: Statistical analysis of DBL2 of FIBRONEER-IPF and final DBL of INPULSIS, Time to First Acute Exacerbation (Exponential)- No AF cohort (Model 2: Time varying FVCpp (categorical) as the predictor - Summary of Data)[27]; Statistical analysis of DBL2 of FIBRONEER-ILD and final DBL of INBUILD, Time to First Acute Exacerbation (Exponential) for PPF no AF cohort (Model 2: Time varying FVCpp (categorical) as the predictor – Summary of Data)[28]
All four trials pooled numbers (i.e. last four table columns) were calculated by summing up IPF and PPF results.

Table 8. Observed Acute Exacerbations in the FIBRONEER-IPF DBL2 and INPULSIS Final DBL Pooled Trial Data by Treatment and by FVC % Predicted Health States

FVC % predicted	Nerandomilast 18 mg bid				Nintedanib 150 mg bid			
	records	patients	events	events/ records	records	patients	events	events/ records
[-Inf,40)	[redacted]							
[40,50)	[redacted]							
[50,60)	[redacted]							
[60,70)	[redacted]							
[70,80)	[redacted]							
[80,90)	[redacted]							
[90, Inf)	[redacted]							
	Placebo FIBRONEER-IPF				Placebo INPULSIS			
	records	patients	events	events/ records	records	patients	events	events/ records
[-Inf,40)	[redacted]							
[40,50)	[redacted]							
[50,60)	[redacted]							
[60,70)	[redacted]							
[70,80)	[redacted]							
[80,90)	[redacted]							
[90, Inf)	[redacted]							

Key: bid, twice a day; DBL, database lock; FVC(pp), forced vital capacity (% predicted); IPF, idiopathic pulmonary fibrosis.
Source: Statistical analysis of DBL2 of FIBRONEER-IPF and final DBL of INPULSIS, Time to First Acute Exacerbation (Exponential) for IPF no AF cohort (Model 3: Treatment and time varying FVCpp (categorical) as predictors - Summary of Data)[27]

Table 9. Observed Acute Exacerbations in the FIBRONEER-ILD DBL2 and INBUILD Final DBL Pooled Trial Data by Treatment and by FVC % Predicted Health States

FVC % predicted	Nerandomilast 18 mg bid				Nintedanib 150 mg bid			
	records	patients	events	events/ records	records	patients	events	events/ records
[-Inf,40)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[40,50)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[50,60)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[60,70)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[70,80)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[80,90)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[90, Inf)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo FIBRONEER-ILD				Placebo INBUILD			
	records	patients	events	events/ records	records	patients	events	events/ records
[-Inf,40)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[40,50)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[50,60)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[60,70)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[70,80)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[80,90)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[90, Inf)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: bid, twice a day; DBL, database lock; FVC(pp), forced vital capacity (% predicted); ILD, interstitial lung disease
Source: Statistical analysis of DBL2 of FIBRONEER-ILD and final DBL of INBUILD, Time to First Acute Exacerbation (Exponential) for PPF no AF cohort (Model 3: Treatment and time varying FVCpp (categorical) as predictors - Summary of Data)[28]

Table 10. Observed Acute Exacerbations in the FIBRONEER-IPF DBL2, FIBRONEER-ILD DBL2, INPULSIS Final DBL and INBUILD Final DBL Pooled Trial Data by Treatment and by FVC % Predicted Health States

FVC % predicted	Nerandomilast 18 mg bid				Nintedanib 150 mg bid			
	records	patients	events	events/ records	records	patients	events	events/ records
[-Inf,40)	[redacted]							
[40,50)	[redacted]							
[50,60)	[redacted]							
[60,70)	[redacted]							
[70,80)	[redacted]							
[80,90)	[redacted]							
[90, Inf)	[redacted]							
	Placebo FIBRONEER-IPF/ILD				Placebo INBUILD/INPULSIS			
	records	patients	events	events/ records	records	patients	events	events/ records
[-Inf,40)	[redacted]							
[40,50)	[redacted]							
[50,60)	[redacted]							
[60,70)	[redacted]							
[70,80)	[redacted]							
[80,90)	[redacted]							
[90, Inf)	[redacted]							

Key: bid, twice a day; DBL, database lock; FVC(pp), forced vital capacity (% predicted); ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.
Source: Statistical analysis of DBL2 of FIBRONEER-IPF and final DBL of INPULSIS, Time to First Acute Exacerbation (Exponential)- No AF cohort (Model 3: Treatment and time varying FVCpp (categorical) as predictors - Summary of Data)[27]; Statistical analysis of DBL2 of FIBRONEER-ILD and final DBL of INBUILD, Time to First Acute Exacerbation (Exponential) for PPF no AF cohort (Model 3: Treatment and time varying FVCpp (categorical) as predictors – Summary of Data)[28]
All four trials pooled numbers were calculated by summing up IPF and PPF results.

B5. PRIORITY. Section 3.3.5, Pages 166-172 (treatment discontinuation).

Please provide additional information on treatment discontinuation. Specifically, please:

- Provide tables with full details of all reasons for treatment discontinuation
- across the clinical trials considered in the submission. Please report these data as n/N (%) and provide the information by treatment arm and type of PF (IPF, PPF) where possible.

Please see Table 11 for a breakdown of participants that prematurely discontinued treatment presented by treatment arm (placebo, nerandomilast 9 mg bid, nerandomilast 18 mg bid and nintedanib 150 mg bid) and by type of PF (FIBRONEER-IPF, INPULSIS-1 and INPULSIS-2 for IPF patients and FIBRONEER-ILD and INBUILD for PPF patients).

Table 11: Proportion of patients and reasons for premature treatment discontinuation before DBL2 ('no AF background therapy' cohort for FIBRONEER studies)

FIBRONEER-IPF				
	Nerandomilast 18 mg bid N = 87	**Nerandomilast 9 mg bid N = 88**	**Placebo N = 87**	**Total N = 262**
Premature treatment discontinuation before DBL2, n (%)	13 (14.9)	20 (22.7)	23 (26.4)	56 (21.4)
Lack of efficacy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by patient, n(%)	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up, n	[redacted]	[redacted]	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
INPULSIS-1				
	Nintedanib 150 mg bid N = 309		**Placebo N = 206**	**Total N = 513**

Premature treatment discontinuation, n (%)	[redacted]	[redacted]	[redacted]
Adverse event, n (%)	[redacted]	[redacted]	[redacted]
Unexpected worsening of disease under study, n (%)	[redacted]	[redacted]	[redacted]
Unexpected worsening of other pre-existing disease, n (%)	[redacted]	[redacted]	[redacted]
Non-compliant with protocol, n (%)	[redacted]	[redacted]	[redacted]
Lost to follow-up, n	[redacted]	[redacted]	[redacted]
Withdrawal by patient, n (%)	[redacted]	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]	[redacted]
INPULSIS-2			
	Nintedanib 150 mg bid N = 329	**Placebo N = 219**	**Total N = 548**
Premature discontinuation from trial medication, n (%)	[redacted]	[redacted]	[redacted]
Adverse event, n (%)	[redacted]	[redacted]	[redacted]
Unexpected worsening of disease under study, n (%)	[redacted]	[redacted]	[redacted]
Unexpected worsening of other pre-existing disease, n (%)	[redacted]	[redacted]	[redacted]
Non-compliant with protocol, n (%)	[redacted]	[redacted]	[redacted]
Lost to follow-up, n (%)	[redacted]	[redacted]	[redacted]
Withdrawal by patient, n (%)	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

FIBRONEER-ILD				
	Nerandomilast 18 mg bid N = 220	Nerandomilast 9 mg bid N = 220	Placebo N = 222	Total N = 662
Premature treatment discontinuation before DBL2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by patient, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up, n	[redacted]	[redacted]	[redacted]	[redacted]
Other, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
INBUILD				
	Nintedanib 150 mg bid N = 332		Placebo N = 331	Total N = 1,010
Premature discontinuation from trial medication, n (%)	[redacted]		[redacted]	[redacted]
Adverse event, n (%)	[redacted]		[redacted]	[redacted]
Protocol deviation, n (%)	[redacted]		[redacted]	[redacted]
Withdrawal by patient, n (%)	[redacted]		[redacted]	[redacted]
Lost to follow-up, n (%)	[redacted]		[redacted]	[redacted]
Other, n (%)	[redacted]		[redacted]	[redacted]

Key: bid, twice a day; DBL, database lock.
Sources: FIBRONEER-ILD CSAP (Table 69.1.1.1)[7]; FIBRONEER-IPF CSAP (Table 47.1.1.1)[23]; INBUILD CTR (Table 10.1.1:1)[29]; INPULSIS-1 CTR (Table 10.1:1)[30]; INPUSLSIS-2 CTR (Table 10.1:1).[31]

As nerandomilast is not currently routinely used in the UK, it is difficult to comment on the generalisability of the treatment discontinuation data presented. The previously described advisory board panel (see response to A5) noted that there have been higher discontinuation rates due to AEs for current AF treatments in real-world practice compared with those reported in the clinical trial setting.[3] This difference is not expected to be seen with nerandomilast given the favourable safety and tolerability profile for nerandomilast 18 mg bid monotherapy compared with

current AF treatments, particularly in diarrhoea rates leading to treatment discontinuation.

B6. PRIORITY. Section 3.3.5, Pages 166-167 (duration of continued treatment benefit following discontinuation).

Please provide further justification and information to support the assumption of one year of continued treatment benefit following discontinuation. Specifically, please:

- Provide additional data and/or analysis of the trial data to support this position. For example, please consider providing descriptive statistics detailing FVC measures at time points before and after treatment discontinuation.

- Consider additional statistical analyses to demonstrate the magnitude and/or duration of continued treatment benefit over time.

To address concerns in TA747 and TA864 about extrapolating indefinite benefit from short-term trial data, an explicit treatment waning framework was added for this technology appraisal in an effort to address uncertainties raised in previous technology appraisals.[32, 33] A similar concern was raised in the TA504 appraisal where the committee concluded that the evidence did not justify assuming a constant mortality benefit for 8 years after discontinuation, and that a constant benefit up to 5 years after discontinuation was a more reasonable assumption. Hence, the current submission employs an extremely conservative approach in comparison to previous economic models submitted to NICE, which limits the extrapolated treatment benefit for nerandomilast.

In the base case, waning is implemented as a step-change 1-year after the end of trial follow-up in the FIBRONEER trials (maximum follow-up in FIBRONEER-IPF and FIBRONEER-PPF: [redacted] and [redacted] years, respectively; the step-change is applied 1-year later, that is at [redacted] and [redacted] years from the start of the follow-up). Up to that point, any residual benefit is assumed to be captured through the extrapolation of the treatment effect estimates derived from the overall population. These extrapolations implicitly incorporate the impact of treatment discontinuations that occurred during the trial follow-up. After this 1-year post–follow-up period, patients who discontinue

active treatment are assumed to receive no further continued benefit (follow BSC transition probabilities immediately). This conservative assumption avoids assuming continued long-term benefit where supporting evidence is not available. Because efficacy extrapolations for patients who remain on active treatment are derived from the overall trial population (so include the effects of observed treatment discontinuation) this approach will potentially underestimate the efficacy of active treatment.

Evidence to inform post-trial persistence of effect is limited because the FIBRONEER trials were not designed to estimate how long any benefit persists after treatment discontinuation. Across both FIBRONEER trials, follow-up is relatively short for informing long-term persistence, and the number of discontinuations is limited (Table 11). Furthermore, discontinuation is unlikely to be random as it may be related to underlying prognosis or changes in disease severity (e.g., tolerability issues, clinical deterioration, or other factors), meaning outcomes observed after stopping treatment could be confounded and difficult to interpret as an unbiased estimate of duration of benefit after discontinuation.

The post-trial period is where evidence becomes sparse, and there is no robust basis to quantify persistence of benefit beyond the observed follow-up, or to justify any specific duration of effect after discontinuation. In addition, the treatment effects of nerandomilast, nintedanib and pirfenidone are derived from analyses in the ITT population, and therefore already incorporate the impact of treatment discontinuations that occurred during the trials within the observed follow-up period. Given these limitations, we do not expect that additional analyses based solely on the FIBRONEER trial data would reliably estimate post-trial benefit persistence.

- Provide full details of each drug's half-life.

The reported terminal half-life for each drug are as follows:

- Approximately 10−17 hours for nerandomilast 18 mg bid[34]
- Between 10−15 hours for nintedanib[35]
- Approximately 2.4 hours for pirfenidone[36]

- Provide detailed clinical validation of the assumption of a 1-year continued treatment benefit following treatment discontinuation.

As described above, the waning that was implemented a step-change 1-year after the end of trial follow-up in the FIBRONEER trials was done because the OS extrapolations implicitly incorporate the impact of treatment discontinuations that occurred during the trial follow-up. The model currently assumes no continued treatment benefit following treatment discontinuation beyond that time period – that is, people who discontinue nerandomilast more than 1-year from the end of trial follow-up are assumed to move directly to BSC efficacy. This is a conservative assumption, because the efficacy of nerandomilast is likely to persist for a short period after treatment discontinuation. This has been supported by clinical opinion in interviews with five English clinical experts and through structured expert elicitation (SEE) from 12 clinicians.[24, 37] All clinicians consulted acknowledged that the timing of loss of treatment effect is highly uncertain. At the same time, clinicians expected any benefit from nerandomilast to persist for a short period beyond treatment discontinuation.

Importantly, the estimates obtained from the SEE analysis also aligned with the base case assumption's mortality outputs that account for waning. For IPF, the modelled OS output lies within the interquartile range of the SEE estimates at both 5 and 15 years (Figure 6). For PPF, the modelled OS output is lower than the SEE estimates but remains within the plausible range, indicating conservative survival estimates in the model (Figure 7). Further details are provided in the SEE report available in the reference pack[24] and the SEE supplementary files submitted alongside these responses.

Figure 6: Modelled OS output and SEE estimates – IPF



Key: BSC, best supportive care; IPF, idiopathic pulmonary fibrosis; OS, overall survival; SEE, structured expert elicitation.
Note: * Includes base case treatment waning assumption (no benefit assumed after the max FIBRONEER-IPF trial follow-up + 1 year; people who discontinue after this initial time period move directly to BSC efficacy)

Figure 7: Modelled OS output and SEE estimates – PPF



Key: BSC, best supportive care; OS, overall survival; PPF, progressive pulmonary fibrosis; SEE, structured expert elicitation.
Note: * Includes base case treatment waning assumption (no benefit assumed after the max FIBRONEER-ILD trial follow-up + 1 year; people who discontinue after this initial time period move directly to BSC efficacy)

To support characterisation of the impact of uncertainty around the duration of treatment effect, additional scenarios are presented below that model treatment effect being lost from various timepoints:

- 50 years: approximates no loss of effect, consistent with the nintedanib appraisals[32, 33, 38] (Table 12 and Table 13)
- 5 years: consistent with the assumption made in the pirfenidone appraisal[39] (Table 14 and Table 15)

In summary, the waning that was implemented a step-change 1-year after the end of trial follow-up in the FIBRONEER trials was done because the OS extrapolations implicitly incorporate the impact of treatment discontinuations that occurred during the trial follow-up – to prevent any double-counting of discontinuation effects. A 1-year time period is a very conservative assumption compared with previous technology appraisals, especially as nerandomilast's efficacy is likely to persist for a

short period after treatment discontinuation, as supported by UK clinicians, and which is currently not captured in the mode. Importantly, modelled mortality inclusive of treatment discontinuation is aligned with clinician expectations from interviews and the SEE, and the additional waning scenarios transparently bracket the plausible range around this reasonable central assumption.

Table 12: Fully incremental results with treatment effect lost at 50 years from model start – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	12,609	4.46	3.40	-	-	-	-
Pirfenidone	13,361	4.82	3.67	752	0.36	0.28	2,705
Nintedanib	[redacted]	4.82	3.67	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	9.21	6.80	[redacted]	4.39	3.12	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 13: Fully incremental results with treatment effect lost at 50 years from model start – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	17,458	4.65	3.32	-	-	-	-
Nintedanib	[redacted]	6.09	4.33	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	7.80	5.45	[redacted]	3.16	2.13	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 14: Fully incremental results with treatment effect lost at 5 years from model start – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	12,609	4.46	3.40	-	-	-	-
Pirfenidone	13,610	4.82	3.67	1,001	0.36	0.27	3,713
Nintedanib	[redacted]	4.82	3.66	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	6.63	5.03	[redacted]	1.82	1.36	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 15: Fully incremental results with treatment effect lost at 5 years from model start – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	17,458	4.65	3.32	-	-	-	-
Nintedanib	[redacted]	5.53	3.96	[redacted]	0.88	0.64	[redacted]
Nerandomilast	[redacted]	6.20	4.44	[redacted]	0.68	0.48	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Health state utility values

B7. Sections 3.4.7.1 and 3.4.7.2 (Pages 182-185) & Economic model, tab: "Utilities", Cell: "G56". Please confirm that when the switch for source of health state utilities is set to "FIBRONEER trial data", that this is applying utilities from the pooled analyses of the FIBRONEER-IPF and IMPULSIS studies for the IPF model and the pooled FIBRONEER-ILD and INBUILD studies for the PPF model. If so, please also provide utility values based on the FIBRONEER trial data alone for scenario analyses.

Thank you for bringing this to our attention. We confirm that when the source of health state utilities is set to 'FIBRONEER trial data' the model applies utility inputs

derived from pooled analyses: FIBRONEER-IPF and INPULSIS for the IPF model, and FIBRONEER-ILD and INBUILD for the PPF model.

Utilities were pooled with INPULSIS and INBUILD because sample sizes within the FIBRONEER trials alone were small. When utilities were estimated using FIBRONEER trial data only, the resulting values were unstable and, for the IPF cohort, produced implausible estimates that were higher than general population utility. The utility values based on FIBRONEER trial data alone are provided in Table 16.

Table 16: Health state utilities from the FIBRONEER trials

FVC % predicted	FIBRONEER-IPF	FIBRONEER-ILD
≥ 110	[redacted]	[redacted]
100–109.9	[redacted]	[redacted]
90–99.9	[redacted]	[redacted]
80–89.9	[redacted]	[redacted]
70–79.9	[redacted]	[redacted]
60–69.9	[redacted]	[redacted]
50–59.9	[redacted]	[redacted]
40–49.9	[redacted]	[redacted]
30–39.9	[redacted]	[redacted]

Key: FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

Table 17 and Table 18 provide the results of the fully incremental analysis for IPF and PPF when using utility values from FIBRONEER only. The scenario has minimal impact on the fully incremental results: ICERs move only marginally versus the base case and the overall conclusions remain unchanged.

Table 17: Fully incremental results using FIBRONEER-IPF utility values – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	12,609	4.46	3.31	-	-	-	-
Pirfenidone	13,625	4.74	3.52	1,016	0.28	0.21	4,824
Nintedanib	[redacted]	4.74	3.52	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	5.96	4.43	[redacted]	1.22	0.91	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 18: Fully incremental results using FIBRONEER-ILD utility values – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	17,458	4.65	3.37	-	-	-	-
Nintedanib	[redacted]	5.26	3.82	[redacted]	0.62	0.45	[redacted]
Nerandomilast	[redacted]	5.74	4.17	[redacted]	0.47	0.35	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Disutility values used in the economic model

B8. PRIORITY. Section 3.4.4, Pages 179-180. Please provide further clarification regarding the disutility values applied in the economic model for IPF and PPF for acute exacerbations. Specifically, please:

- Provide further justification regarding the application of a fixed acute exacerbation disutility across all FVC health states. Where possible, please explore:
    - A regression model with interaction effects by health state to account for the potential greater impact on utility of an acute exacerbation for patients with lower FVC.

During the statistical analyses of trial-based health state utility values, a model with interaction terms between FVC % predicted and history of acute exacerbation was also explored. Results are shown for IPF in Table 19 and Figure 8; and PPF in Table 20 and Figure 9 below. All interaction terms included resulted in coefficient estimates not statistically significant and without any clear pattern showing a relationship between FVC % predicted and QoL decrement due to history of acute exacerbation.

The likelihood ratio test assessing the overall interaction effect was statistically significant at the 10% level for IPF. However, as illustrated in Figure 8, the direction of the predicted utility values across FVC % predicted categories appears counterintuitive, among patients with a history of exacerbations. Specifically, higher FVC % predicted categories (e.g., [80,Inf)) were associated with lower predicted utility values, which is not clinically plausible and contradicts clinical expectations. This unexpected pattern is likely ascribable to the limited number of observed exacerbation events, leading to unstable estimates for the interaction terms. Consequently, interaction terms were not retained in the final model.

Similarly, for PPF, the combined p-value was not significant, and a similar counterintuitive direction was observed (Figure 9).

Table 19. Utility analyses results in the IPF population – testing for interaction of FVC % predicted and history of acute exacerbation

Term	Estimate	LCI	UCI	SE	Statistic	P-value
(Intercept)	[redacted]	[redacted]	[redacted]	0.023	5.909	<0.001
base_UK	[redacted]	[redacted]	[redacted]	0.018	36.571	<0.001
fvcpp_cat[40,50)	[redacted]	[redacted]	[redacted]	0.019	4.350	<0.001
fvcpp_cat[50,60)	[redacted]	[redacted]	[redacted]	0.019	6.679	<0.001
fvcpp_cat[60,70)	[redacted]	[redacted]	[redacted]	0.019	7.932	<0.001
fvcpp_cat[70,80)	[redacted]	[redacted]	[redacted]	0.019	8.331	<0.001
fvcpp_cat[80, Inf)	[redacted]	[redacted]	[redacted]	0.019	9.499	<0.001
history.exac.30days	[redacted]	[redacted]	[redacted]	0.070	-0.083	0.9336
fvcpp_cat[40,50):history.exac.30days	[redacted]	[redacted]	[redacted]	0.088	0.819	0.4126
fvcpp_cat[50,60):history.exac.30days	[redacted]	[redacted]	[redacted]	0.079	-0.274	0.7843
fvcpp_cat[60,70):history.exac.30days	[redacted]	[redacted]	[redacted]	0.099	-0.385	0.7001
fvcpp_cat[70,80):history.exac.30days	[redacted]	[redacted]	[redacted]	0.083	-0.071	0.9438
fvcpp_cat[80, Inf):history.exac.30days	[redacted]	[redacted]	[redacted]	0.080	-1.550	0.1213
fvcpp_cat:history.exac.30days (LRT)	[redacted]	[redacted]	[redacted]	NA	NA	0.0662

Key: FVC % predicted, forced vital capacity percent predicted; LCI, lower confidence interval; SE, standard error; UCI, upper confidence interval.

Source: Statistical analysis using DBL2 from FIBRONEER-IPF and INPULSIS trial data[40]

Figure 8. Predicted utility values in the IPF cohort by FVC % predicted and exacerbation history based on model with interactions



Source: Statistical analysis using DBL2 from FIBRONEER-IPF and INPULSIS trial data[40]

Table 20. Utility analyses results in the PPF population – testing for interaction of FVC % predicted and history of acute exacerbation

Term	Estimate	LCI	UCI	SE	Statistic	P-value
(Intercept)	[redacted]	[redacted]	[redacted]	0.019	5.559	<0.001
base_UK	[redacted]	[redacted]	[redacted]	0.018	34.736	<0.001
fvcpp_cat[40,50)	[redacted]	[redacted]	[redacted]	0.014	4.697	<0.001
fvcpp_cat[50,60)	[redacted]	[redacted]	[redacted]	0.014	8.632	<0.001
fvcpp_cat[60,70)	[redacted]	[redacted]	[redacted]	0.015	10.722	<0.001
fvcpp_cat[70,80)	[redacted]	[redacted]	[redacted]	0.015	12.185	<0.001
fvcpp_cat[80, Inf)	[redacted]	[redacted]	[redacted]	0.016	13.335	<0.001
history.exac.30days	[redacted]	[redacted]	[redacted]	0.050	-1.548	0.1216
fvcpp_cat[40,50):history.exac.30days	[redacted]	[redacted]	[redacted]	0.066	0.055	0.9562
fvcpp_cat[50,60):history.exac.30days	[redacted]	[redacted]	[redacted]	0.067	0.750	0.4534
fvcpp_cat[60,70):history.exac.30days	[redacted]	[redacted]	[redacted]	0.064	-1.244	0.2136

Term	Estimate	LCI	UCI	SE	Statistic	P-value
fvcpp_cat[70,80):history.exac.30days	[redacted]	[redacted]	[redacted]	0.083	-1.695	0.0901
fvcpp_cat[80, Inf):history.exac.30days	[redacted]	[redacted]	[redacted]	0.078	-0.052	0.9587
fvcpp_cat:history.exac.30days (LRT)	[redacted]	[redacted]	[redacted]	NA	NA	0.1367

Key: FVC % predicted, forced vital capacity percent predicted; LCI, lower confidence interval; SE, standard error; UCI, upper confidence interval.

Source: Statistical analysis using DBL2 from FIBRONEER-ILD and INBUILD trial data[41]

Figure 9. Predicted utility values in the PPF cohort by FVC % predicted and exacerbation history based on model with interactions



Source: Statistical analysis using DBL2 from FIBRONEER-ILD and INBUILD trial data[41]

- A regression model that does not include a parameter for acute exacerbation to directly inform health state utility values in the model.

As requested, the utility analyses was repeated without including history of acute exacerbation as predictor for IPF and PPF, with results provided in Table 21 and Table 22, respectively. Table 23 shows the resulting health state utility values, demonstrating that excluding history of acute exacerbation has a limited (negative) impact. Please note that previous economic models have also included disutility value for acute exacerbation, both short and long-term for IPF[20] and short-term only for PPF.[33]

Table 21. Utility analyses results in the IPF population – without including history of acute exacerbation as predictors

Term	Estimate	LCI	UCI	SE	Statistic	P-value
(Intercept)	[redacted]	[redacted]	[redacted]	0.023	5.936	<0.001
base_UK	[redacted]	[redacted]	[redacted]	0.018	36.645	<0.001
fvcpp_cat[40,50)	[redacted]	[redacted]	[redacted]	0.019	4.51	<0.001
fvcpp_cat[50,60)	[redacted]	[redacted]	[redacted]	0.019	6.796	<0.001
fvcpp_cat[60,70)	[redacted]	[redacted]	[redacted]	0.019	8.087	<0.001
fvcpp_cat[70,80)	[redacted]	[redacted]	[redacted]	0.019	8.497	<0.001
fvcpp_cat[80, Inf)	[redacted]	[redacted]	[redacted]	0.018	9.651	<0.001

Key: FVC % predicted, forced vital capacity percent predicted; LCI, lower confidence interval; SE, standard error; UCI, upper confidence interval.

Source: Statistical analysis using DBL2 from FIBRONEER-IPF and INPULSIS trial data[40]

Table 22. Utility analyses results in the PPF population – without including history of acute exacerbation as predictors

Term	Estimate	LCI	UCI	SE	Statistic	P-value
(Intercept)	[redacted]	[redacted]	[redacted]	0.019	5.320	<0.001
base_UK	[redacted]	[redacted]	[redacted]	0.018	34.688	<0.001
fvcpp_cat[40,50)	[redacted]	[redacted]	[redacted]	0.013	5.141	<0.001
fvcpp_cat[50,60)	[redacted]	[redacted]	[redacted]	0.014	9.191	<0.001
fvcpp_cat[60,70)	[redacted]	[redacted]	[redacted]	0.014	11.223	<0.001
fvcpp_cat[70,80)	[redacted]	[redacted]	[redacted]	0.015	12.726	<0.001
fvcpp_cat[80, Inf)	[redacted]	[redacted]	[redacted]	0.015	13.898	<0.001

Key: FVC % predicted, forced vital capacity percent predicted; LCI, lower confidence interval; SE, standard error; UCI, upper confidence interval.

Source: Statistical analysis using DBL2 from FIBRONEER-ILD and INBUILD trial data[41]

Table 23: Health state utilities without including history of acute exacerbation as predictors

FVC % predicted	FIBRONEER-IPF	FIBRONEER-ILD
≥ 110	[redacted]	[redacted]
100–109.9	[redacted]	[redacted]

FVC % predicted	FIBRONEER-IPF	FIBRONEER-ILD
90–99.9	[redacted]	[redacted]
80–89.9	[redacted]	[redacted]
70–79.9	[redacted]	[redacted]
60–69.9	[redacted]	[redacted]
50–59.9	[redacted]	[redacted]
40–49.9	[redacted]	[redacted]
30–39.9	[redacted]	[redacted]
Key: FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.		

- Double check the confidential marking for disutilities for acute exacerbations. Tables 53 and 54 show confidential marking for the disutilities derived from the pooled FIBRONEER-IPF / INPULSIS studies and FIBRONEER-ILD / INBUILD analyses respectively. However, the corresponding text on Page 179 does not show confidential marking.

Thank you for highlighting the confidential marking discrepancy associated with acute exacerbation disutility. We have reviewed the marking applied to the disutility values for acute exacerbations derived from the pooled FIBRONEER-IPF / INPULSIS studies and the FIBRONEER-ILD / INBUILD analyses. Tables 53 and 54 are correctly marked as confidential. The corresponding narrative text on page 179 should also have been marked as confidential, but this was omitted in error. No changes are required to the values presented, and this is a marking correction only.

'For IPF, a disutility value of [redacted] is applied, derived from pooled INPULSIS final DBL and FIBRONEER-IPF DBL2 data.'

'For PPF, a disutility value of [redacted] is applied, derived from pooled INBUILD final DBL and FIBRONEER-ILD DBL2 data.'

Correct CIC marking has been applied in the corrected company submission document re-submitted alongside clarification questions responses.

B9. Section 3.4.6, Pages 181-182 (disutility of liver function tests). Please provide further details and justification for the application of a disutility for liver function tests in the economic model. Specifically, please:

- Provide further reassurance that this disutility has not already been captured by the health state utilities and that the risk of double-counting is minimal.

The health state utilities used in the economic model are derived from EQ-5D results from patients who participated in randomised controlled trials (RCT), specifically FIBRONEER-IPF, FIBRONEER-ILD, INPULSIS and INBUILD. It is widely acknowledged that that care received in an RCT setting is subject to rigorous quality standards with organised facilitation of diagnostic testing, medical support, and regular contact with a healthcare professional.[42, 43] RCT sites tend to also be located in urban areas at specialist centres and recruit patients within that geographic area; in a real-world setting, a significant proportion of patients IPF or PPF do not live within close proximity to specialist ILD centres, which contributes to the quality of life burden associated with these diseases.[44, 45] Therefore, the company is confident that the real-world quality of life impact (captured as a disutility in the economic model) associated with accessing liver function testing as part of the routine monitoring for patients receiving currently available antifibrotics (AF) is not captured in the health state utility values used in the economic modelling.

As described in Section 3.4.6 of the CS, it is on this basis that the company considers it appropriate to add an additional disutility for liver function testing in the economic model to quantitatively capture this lived reality for patients receiving current AF treatments for IPF and PPF. By not doing this, the company is concerned that the burden associated with liver function tests for patients with IPF and PPF will not be adequately reflected in the economic modelling and, therefore, miss a crucial aspect of the patient experience. The potential for nerandomilast to reduce liver function tests was repeatedly emphasised during clinical validation as one of the most meaningful differentiators in practice, given both patient burden and the operational implications for services.[37] Patients often describe ongoing monitoring as a ‘constant reminder of illness,’ contributing to treatment fatigue – an aspect not otherwise captured. Patients also consistently describe routine liver function tests as disruptive and anxiety-provoking, particularly when linked to treatment continuation

or side-effect monitoring. While not altering underlying health status, these emotional and practical burdens meaningfully shape patients' lived experience and therefore justify a separate disutility.

- Comment on the validity of the assumption that the disutility of an IV infusion is generalisable to the patient experience of receiving a liver function test.

As described in the CS, no published evidence has been identified that directly quantifies a disutility associated with liver function testing. This evidence gap is expected, as the burden of monitoring procedures is rarely studied in isolation. However, patient feedback consistently highlights that regular monitoring obligations themselves – regardless of the procedure – carry emotional and logistical impact. This strengthens the rationale for applying a proxy disutility.

Therefore, an alternative source was used based on the intravenous (IV) infusion disutility used in TA898. The input used in TA898 included the disutility of three infusions but was adjusted for the economic modelling in this case to a single infusion to make this disutility generalisable to the patient experience of IPF and PPF. Although liver function tests are less intensive than infusions, both require healthcare attendance, scheduling, planning and generate anticipatory anxiety. Using a single-infusion disutility represents a conservative and proportionate estimate of monitoring burden without overstating impact.

The company acknowledges that there are limitations associated with this approach but in the absence of alternative evidence, considered this appropriate for inclusion in the company base case analysis.

To assess the impact of this input on the overall cost-effectiveness results, a scenario analysis has been conducted removing this disutility from the analysis.

Table 24 and Table 25 present the fully incremental results excluding liver function tests disutility. Excluding liver function tests disutility had minimal impact on results. As expected, only QALYs (and therefore ICERs) changed slightly, with no change to the fully incremental ordering or dominance conclusions.

In IPF, the pirfenidone versus BSC comparison increased by 0.01 incremental QALYs (0.21 to 0.22), reducing the ICER from £4,831 to £4,533/QALY; nintedanib remained strictly dominated. The nerandomilast versus pirfenidone comparison decreased by 0.01 incremental QALYs (0.93 to 0.92), increasing the ICER marginally from [redacted] to [redacted]/QALY. In PPF, the nintedanib versus BSC comparison increased by 0.01 incremental QALYs (0.45 to 0.46), reducing the ICER from [redacted] to [redacted] QALY. The Nerandomilast versus nintedanib comparison decreased by 0.02 incremental QALYs (0.35 to 0.33), increasing the ICER marginally from [redacted] to [redacted]/QALY.

Overall, the scenario changes were small and did not affect the existing conclusions.

Table 24: Fully incremental results excluding liver function tests disutility – PAS prices; IPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	12,609	4.46	3.40	-	-	-	-
Pirfenidone	13,625	4.74	3.62	1,016	0.28	0.22	4,533
Nintedanib	[redacted]	4.74	3.62	[redacted]	-	-	[redacted]
Nerandomilast	[redacted]	5.96	4.54	[redacted]	1.22	0.92	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 25: Fully incremental results excluding liver function tests disutility – PAS prices; PPF

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	17,458	4.65	3.32	-	-	-	-
Nintedanib	[redacted]	5.26	3.79	[redacted]	0.62	0.46	[redacted]
Nerandomilast	[redacted]	5.74	4.12	[redacted]	0.47	0.33	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year.

B10. Section 3.4.5, Pages 180-181, Table 55 & Economic model file. Table 55 suggests that disutilities are applied over 13.04 weeks duration, whereas the economic model, tab: 'utilities', cells: 'I38:I43' suggests a disutility duration for adverse events of 4.35 weeks. Please clarify the apparent discrepancy and confirm the company's preferred approach to modelling adverse event disutilities.

Thank you for bringing this to our attention. We have reviewed the AE disutility durations presented in the dossier and implemented in the economic model. The 13.04-week duration shown in Table 55 is a mislabelling/incorrect statement in the dossier and does not reflect what is implemented in the model.

The company's approach is to model AE disutilities over 4.35 weeks, consistent with the approach used in the model and aligned with previous EAG preferences expressed during previous nintedanib appraisals (TA747; TA864).[32, 33] No changes to the model or results are required, as the model already applies the correct 4.35-week duration; the discrepancy is limited to the dossier reporting. To avoid confusion, this has been amended in the corrected company submission document re-submitted alongside clarification questions responses.

Concomitant medications

B11. Section 2.10.2, Pages 88-93. Please provide a table giving full details (medication name and proportion receiving treatment) of all concomitant medications used in the key clinical effectiveness studies, by treatment arm, for nintedanib, pirfenidone and nerandomilast. Please comment on their relevance to UK clinical practice and provide a scenario analysis with their inclusion in the economic model.

Nearly all patients in FIBRONEER-IPF, FIBRONEER-ILD, INBUILD and INPULSIS trials received one or more concomitant medication at baseline or on-treatment (Table 26 and Table 27).

Table 26: Patients with at least one concomitant medication at baseline or on−treatment in the FIBRONEER trials ('no AF background therapy' cohort)

	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo	Total
FIBRONEER-IPF				
N	[redacted]	[redacted]	[redacted]	[redacted]
≥1 baseline or on-treatment concomitant medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
FIBRONEER-ILD				
N	[redacted]	[redacted]	[redacted]	[redacted]
≥1 baseline concomitant medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥1 baseline or on-treatment concomitant medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: AF, antifibrotic; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis
Source: FIBRONEER-IPF CSAP (Table 47.1.3.1.1)[23]; FIBRONEER-ILD CSAP (Table 69.1.3.3.2).[7]

Table 27: Patients with at least one concomitant medication at baseline or on−treatment in INBUILD and INPULSIS

	Nintedanib 150 mg bid	Placebo	Total
INBUILD			
N	[redacted]	[redacted]	[redacted]
≥1 baseline or on-treatment concomitant medication, n (%)	[redacted]	[redacted]	[redacted]
INPULSIS			
N	[redacted]	[redacted]	[redacted]
≥1 baseline or on-treatment concomitant medication, n (%)	[redacted]	[redacted]	[redacted]

Key: AF, antifibrotic; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis
Source: INBUILD CTR (Table 10.4.6.1: 1)[29]; INPULSIS 1 CTR (Table 15.1.4.3.1.2: 1)[30]; INPULSIS 2 CTR (Table 15.1.4.3.1.2: 1)[31]

Full details of all concomitant medications used in the FIBRONEER, INBUILD and INPULSIS trials can be found in the FIBRONEER-IPF CSAP (Table 47.1.3.1.1)[23], the FIBRONEER-ILD CSAP (Table 69.1.3.3.2)[7], the INBUILD CTR (Table 10.4.6.1: 1)[29], and the INPULSIS 1 & 2 CTRs (Table 15.1.4.3.1.2: 1).[30, 31] Baseline concomitant medication use was well balanced both between treatment groups of individual FIBRONEER, INPULSIS and INBUILD trials and across trials. In terms of relevance to UK clinical practice, the only concern raised by experts consulted was in relation to concomitant immunosuppressants use – please see full discussion of this in the response to question A6.

Concomitant medication use is not reported in the ASCEND or CAPACITY trial publications[22, 46] and we do not have access to the clinical trial reports for these studies. As concomitant medication use was not a topic of discussion in the committee meeting for TA504, we assume there were no comparability or generalisability concerns raised in relation to concomitant medication use.

Given there are no clear and meaningful differences in concomitant medication use observed across treatment arms, we have not included them in the economic model. Total costs would be similar across all arms, with limited impact on incremental costs. Any residual incremental difference would be expected to arise primarily through differences in any additional years of life lived (i.e., longer survival leading to additional background medication accrual). These additional costs would be discounted over time, and the duration of concomitant medications is unclear; both aspects would further reduce their impact on the incremental results.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis [ID6446]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Action for Pulmonary Fibrosis (APF)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	APF is a UK-wide charity that offers support to all who are affected by PF. We bring people together to drive change so more people affected by pulmonary fibrosis (or lung scarring) can live well for longer. People living with lung scarring, their loved ones and the professionals caring for them are at the heart of everything we do. APF provide expert support, information, education, help a growing network of support groups and raise awareness of pulmonary fibrosis. We collaborate to drive change that improves health and care and we provide vital resources to researchers, bringing hope for new and future treatments for this devastating disease.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	APF has received the following funding from Boehringer Ingelheim in the previous 12 months: £75,000 grant towards the OneVoiceILD movement. Grants towards this programme are given on an arms' length basis and grant givers are not given anything in return. £12,000 for sponsorship of APF's pulmonary fibrosis awareness month campaign. Around £17,000 for consultancy fees to provide consultancy services on specific projects on policy development, involving patients in trial design, and patient reviews of documentation.

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Last year (2025) APF conducted a UK-wide lived experience survey of those living with PF, with a loved one/caring for someone living with PF, or bereaved by PF. Over 1250 individuals responded to the survey, which focused on obtaining quantitative data regarding experiences and outcomes of PF services in the UK. All forms of PF were included, with respondents self-reporting their individual diagnoses. Those living with IPF made up 67% of the cohort, with the remainder being PPF. The survey opened on 14th May and closed on 30th June 2025. The full report of the PF State of the Nation survey will be published on 25th February 2026. Other, sex and subtype-specific findings are outlined in a research paper co-authored by APF, titled Patient-Reported Experiences of Pulmonary Fibrosis in the UK: The role of sex and disease subtypes in symptomology, diagnosis and care (Massen, G. et al.) which is being submitted to the Therapeutic Advances in Respiratory Disease journal for publication. We are happy to provide an embargoed copy of this if helpful. Qualitative data was collected in 2023 through a UK-wide lived experience survey, the findings of which were published in the I Wish it was Cancer report in December 2023. This survey also encapsulated the views of those living with, caring for, or bereaved by PF in the UK. Any qualitative data or testimony shared here can be found published within this report. As a support charity, we also offer support groups and a support line to all who are affected by PF. We receive anecdotal feedback from these platforms.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Pulmonary fibrosis is a terminal diagnosis and debilitating condition. As the condition progresses, tightening and hardening of the lungs makes it increasingly difficult to breathe. Movement becomes restricted by the growing effort required for even simple activities, turning everyday tasks such as walking short distances, climbing stairs, or getting dressed into exhausting challenges. Many people describe a persistent sense of air hunger, anxiety linked to breathlessness, and a loss of independence that can impact emotional wellbeing as much as physical health. Our survey found that those living with PF face a myriad of challenges from onset of symptoms onwards. The most common symptoms of PF are breathlessness (66%), chronic cough (53%), fatigue (32%), and unexplained weight loss (5%). Of those with IPF, 90% are symptomatic prior to diagnosis, and 46% have multiple symptoms. Over time, living with PF means adapting to a slower pace of life while coping with isolation and a terminal prognosis with no clear timeline. For those who progress to the point of needing oxygen therapy, ambulatory oxygen can support their mobility but also impact the logistics of leaving the house – including to attend hospital appointments that may be many miles away.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Currently, treatment options for pulmonary fibrosis are limited. Available pharmacological treatments are not curative and may only slow lung function decline for some people. This is alongside supportive care to help manage symptoms and support quality of life. Both pirfenidone and nintedanib offer variable benefit and are generally not well tolerated. Anecdotally, we hear from the clinical community that as many as 40% of those on antifibrotics are forced to cease treatment due to side effects.

	In our recent survey, of those currently receiving antifibrotic treatment, 16% reported experiencing only one side-effect whilst 75% reported multiple symptoms. The most common were diarrhoea (58%), decreased appetite (52%), nausea (50%), stomach pain (46%). Lesser-reported symptoms included vomiting (18%), headache (14%), liver problems (6%), high blood pressure (5%) and sun sensitivity (1%). Diarrhoea was deemed to be the symptom that had the most significant impact on quality of life by 38% of those affected. Anecdotally, those for this side effect talk of this as a particularly debilitating side effect, with many needing to stay close to a toilet, causing some to withdraw from their social lives. Supportive therapies play an important role in managing symptoms and improving overall wellbeing. Pulmonary rehabilitation, for example, helps people cope with breathlessness and the anxiety or panic that often accompanies it. This can reduce reliance on already over-stretched specialist and emergency services, yet access remains limited for many. Waiting times are often long, and some people die from the disease before receiving this support. Psychological care is also essential in helping individuals manage the isolation associated with the condition, its life-limiting prognosis, and the side effects of the only available treatments, all of which can significantly affect quality of life. Despite this need, 72% of people bereaved by pulmonary fibrosis report that their loved one died without being able to access psychological support services through the NHS. Current treatments also require regular liver function testing, which is a significant burden for patients living with a life-altering and debilitating condition that significantly impacts mobility.
8. Is there an unmet need for patients with this condition?	There is huge unmet need for those living with PF. There is no cure for the condition, a high and symptom burden, and an unpredictable rate of disease progression. Patients face not only debilitating physical challenges that affect their daily life but also carry the psychological weight of uncertainty regarding their future. For many, the existing medications take their own toll, with adverse effects causing a high discontinuation rate. Some do not feel that the varying levels of effectiveness of the drug in slowing lung function decline is worth the further drop in their quality of life. Limited and unequal access to supportive therapies further exacerbates the challenges patients face, predominantly alone, and unsupported by a system that is not fit for purpose to meet their needs. Even obtaining a diagnosis to be able to be considered for treatment is a huge challenge. Delays to diagnosis are considerable and system-wide, with accumulative waits at each stage of the care pathway. In England, 47% of those with IPF waited over 6months for a diagnosis and nearly a third (32%) waited over 1 year. Of those with PPF, 52% waited over 6months and 37% waited over 1 year. 16% reported having to report their symptoms to a GP over 5 times before even being referred and those in England wait longer to then see a specialist than patients in the rest of the devolved nations. Misdiagnosis is high – 1 in 3 (32%) of PF patients in England are misdiagnosed at least once and 71% of those who are receive treatment for their incorrect diagnosis before their condition is confirmed as PF. This not only leads to uncertainty and potential exacerbation of their condition due

	to incorrect medications but also allows the condition to progress unchecked when they could be receiving life-lengthening treatment.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	For those facing a terminal prognosis, living better for longer is what they hope for most. Nintedanib and pirfenidone can offer this to some, but this is not the reality for many receiving the treatment. Side-effects are so debilitating that adherence remains high. We have anecdotal reports from ILD healthcare professionals that around 40% of patients will cease the treatment due to adverse effects. This patient group are therefore never reaching the point where they experience any of the long-term benefits. The introduction of a novel therapy provides a new sense of hope that hasn't been felt in over a decade. At the very least, ~40% of patients who discontinue current drug therapies due to adverse effects would have the opportunity to see long-term benefits accrue from increased time on treatment – both increasing time to mortality and improving their quality of life during the time they have left. Both nintedanib and pirfenidone are to be taken with or immediately after meals. This can pose its own challenge as PF can cause loss of appetite, and the medications can cause nausea, which leads to loss of appetite. Dietetics support is difficult to access, so this becomes another challenge within the patient and carer journey. Nerandomilast does not need to be taken with or immediately after food. A lighter side-effect burden and an improved quality of life would alleviate some of the pressures and anxieties for carers who commit their time and energy to helping their loved ones to live better for longer. Whilst current treatments require regular liver function testing (a significant burden for patients), we believe only base tests are required for nerandomilast. This will improve the burden associated with antifibrotic treatment.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	There are groups who are eligible for antifibrotic medication who have either tried both drug options (pirfenidone and nintedanib) and been unable to tolerate them, or who have not seen the same clinical benefit as others. For these individuals, an alternative drug that could be utilised instead of, existing antifibrotic drug options could mean the difference between ceasing and continuing life-extending treatment. Diarrhoea is reported to be the most life-affecting side effect of antifibrotics and is more prevalent in those who are younger at point of diagnosis (p=0.041), therefore this group may benefit more from this drug option.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There are location-based inequalities in access to existing treatment. In England, care for PF is delivered through specialist Interstitial Lung Disease (ILD) services, and antifibrotic therapies can currently be prescribed only from 24 specialist ILD centres nationwide. This centralisation creates capacity bottlenecks, meaning patients referred to specialist centres may face prolonged waits to be assessed by already over-stretched expert teams. It also leads to tiered access, with those living closest to a specialist centre often receiving more timely care. Patients frequently describe access to treatment and supportive services as a “postcode lottery,” where geographical location determines the quality, availability, and timeliness of care they receive. Led by OneVoiceILD and Action for Pulmonary Fibrosis, work is underway to improve access to treatments through a regional model of care. This is reflected in the OneVoiceILD national integrated care pathway, the structure for which will be set out through a new service specification.

Other issues

13. Are there any other issues that you would like the committee to consider?	People living with PF have been left behind as treatments for other chronic lung diseases have continued to advance. The current model of care is not fit for purpose, leaving patients’ needs unmet at multiple stages of the care pathway. Stakeholders, including APF, have worked tirelessly to address these systemic challenges and to ensure that people with PF can access treatment as quickly as possible. The emergence of an alternative therapy demonstrating improved tolerability, sustained long-term effectiveness offers a long-awaited source of hope that this patient community desperately needs.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Pulmonary fibrosis is a hugely debilitating terminal disease that robs individuals of their breath, independence and life. • Nerandomilast has been shown to be effective and is the first new treatment in this indication for over a decade. • Current treatments have limited efficacy in slowing progression, and have generally poor tolerability with a high rate of discontinuation. • The introduction of an efficacious, better tolerated drug offers the opportunity for those with PF to continue on the drug for longer, accrue health benefits as a result, and ultimately live better for longer. • We strongly support the approval of this medicine to address the significant unmet need in PF.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis [ID6446]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of Respiratory Nurses
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of Respiratory Nurses (ARNS) was established in 1997 as a nursing forum to champion the specialty respiratory nursing community, promote excellence in practice, and influence respiratory health policy. ARNS also works to influence the direction of respiratory nursing care. The organisation is funded via member subscriptions and supported by partner organisations including Boehringer Ingelheim, Astrazeneca, Chiesi, GSK and Trudell Medical UK.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes. ARNS has received funding from Boehringer Ingelheim in the past 12 months. The funding amount was £18,500 + VAT, and this included a large exhibition stand at the ARNS Conference 2025, a direct mailshot to HCPs on the ARNS mailing list, and promotion of Boehringer Ingelheim on the ARNS monthly e-shot.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To slow progression of pulmonary fibrosis.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduced decline in lung function, as measured by FVC. Maintained/improved quality of life. Maintained or improved symptom burden. Maintained or improved exercise tolerance. Increased survival.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Symptom burden is high and prognosis is poor. Treatment is currently limited to two medications (Pirfenidone and Nintedanib) which can have significant side effects and are frequently intolerable.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Anti-fibrotics (Pirfenidone and Nintedanib), immunosuppressants, steroids, adjunct treatments such as oxygen, mucolytics, opiods, anxiolytics. Supportive care via a multidisciplinary team (physiotherapists, occupational therapists, dietitians)
9a. Are any clinical guidelines used in the	Yes. NICE guidelines, as listed in the final scope document.

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is well defined, however there is significant regional variation and ongoing delays in diagnosis and treatment nationally, as captured by the work of the patient group, Action for Pulmonary Fibrosis.
9c. What impact would the technology have on the current pathway of care?	It is likely that Nerandomilast can be offered alongside other anti-fibrotics in the current pathway. If a tiering system is implemented in the future, as anticipated, consideration will need to be given as to whether Nerandomilast will be prescribed by Tier 2 centres or just Tier 3 (specialist ILD network hub) centres.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	High-cost medications are currently prescribed in ILD specialist centres, and this is where Nerandomilast is likely to sit best.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Depending on the volume of eligible patients, sites may need further support for MDT diagnosis/eligibility confirmation and non-medical prescribing.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes- as a further treatment option, particularly for patients that cannot tolerate Nintedanib or Pirfenidone.
11a. Do you expect the technology to increase length of life more than current care?	Unknown.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Potentially, if Nerandomilast has fewer side effects.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Nerandomilast is likely to be similar to current care.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Currently patients require baseline lung function tests prior to starting anti-fibrotics, however routine lung function tests are already part of standard care.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Patients with IPF/PPF often have a significant disease burden and median life expectancy is commonly cited as 3-5 years. In these circumstances, the EQ-5D may not be sensitive enough to capture all benefits. A tool based on the capabilities approach (such as the ICECAP tool) might be more useful in capturing broader health-related benefits.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Over the last ten years, clinical research in IPF have yielded largely negative results. This means the positive results of the Nerandomilast trial holds significance.
16a. Is the technology a 'step-change' in the management of the condition?	Benefits appear to be similar to current anti-fibrotic treatments, but Nerandomilast may be better tolerated.

16b. Does the use of the technology address any particular unmet need of the patient population?	It offers a potential alternative treatment in an area where treatment options are very limited. It would be particularly important to patients for whom other treatments are contraindicated or intolerable.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, including standard of care (Nintedanib or Pirfenidone).
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Long-term mortality is important to patients and could not be examined within the scope of the trial follow up period. Quality of life is also an important patient-centred measure. No significant impact was noted within the trial.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical	Unknown.

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA379, TA504, TA747, TA864]?	
21. How do data on real-world experience compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Access for socially/geographically isolated patients if prescribing is restricted to highly specialist centres
22b. Consider whether these issues are different from issues with current care and why.	These issues are not different from current care.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Nerandomilast represents a significant new treatment option for people with IPF/PPF • Nerandomilast will be particularly useful for people unable to tolerate curent anti-fibrotics • Nerandomilast is likely to fit into current care pathways, but further support for MDT diagnosis/eligibility confirmation and non-medical prescribing may be needed • The lack of impact on quality of life measures means that supportive care will remain a key part of treatment for people with IPF/PPF •

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Single Technology Appraisal

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis [ID6446]

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **the deadline in the accompanying email.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Sophie Fletcher
2. Name of organisation	University Hospital Southampton
3. Job title or position	Respiratory consultant & honorary Associate Professor of respiratory medicine with a specialist interest in interstitial lung disease
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis? ☐ A specialist in the clinical evidence base for idiopathic pulmonary fibrosis or progressive pulmonary fibrosis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

8. What is the main aim of treatment for idiopathic pulmonary fibrosis or progressive pulmonary fibrosis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Treatment options for those with idiopathic pulmonary fibrosis included supportive such as provision of oxygen and palliative care, the pharmaceutical such as Pirfenidone and nintedanib which aims to slow not holt nor reverse disease progression and for a small proportion of patients there is the option of lung transplantation. For patients with progressive pulmonary fibrosis if there is an underlying driver of their disease such as an autoimmune process or an environmental precipitant these need to be addressed, in the examples noted above this will be immunosuppression and environmental change. These patients also have access to the therapeutic options available to those with IPF aside from Pirfenidone.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	The slowing of disease progression as measured by a combination of pulmonary function tests, radiology (cross-sectional imaging) and stability of patient's symptoms.
10. In your view, is there an unmet need for patients and healthcare professionals in idiopathic pulmonary fibrosis or progressive pulmonary fibrosis?	There are no pharmaceutical options available that can holt or reverse the disease. The two anti fibrotic medications are available, nintedanib and Pirfenidone, often have side-effects that effect patient tolerance where many patients have the quality of life significantly impaired or are not able to continue with treatment.
11. How is idiopathic pulmonary fibrosis or progressive pulmonary fibrosis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	patients with idiopathic pulmonary fibrosis diagnosed and managed as per clinical guidelines CG163 Guidance for prescription of use of Pirfenidone is available through technology appraisal 504 (TA 504) & nintedanib has been reviewed through technology appraisals (TA 379, T864) Patients currently gain access to both medications having been referred to a specialist centre for interstitial lung disease. The case is discussed in the ILD

across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	MDT to ensure the diagnosis is accurate. If they are eligible for an anti fibrotic medication as per the guidelines noted above, prescription of these medications taken on by the prescribing centre, currently the specialist centres for interstitial lung disease. The Pathway is well-defined. Given that there are relatively few specialist centres for ILD nationally, and the guidelines are clear, there is little variation in approach to diagnosis and management. Patients however, need to be referred to specialist centres to gain access to these anti fibrotic medications, this results in those being at a distance or unable to travel being disadvantaged. This is well documented by the work of action for pulmonary fibrosis. If a new medication fibrosis is made available to the ILD community, I suspect that it will initially be made available to ILD specialist centres and therefore will not have any significant impact to the current pathway.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	If this new medication was available to patients with ILD via ILD specialist centres, it would provide a further option of care to those who fulfilled the criteria for anti fibrotic treatment. The infrastructure is already present to support a new such medication from the ILD specialist centres. This is an oral medication which can be coordinated by the ILD pharmacy services already available in ILD specialist centres.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	This novel anti fibrotic medication offers a new pharmaceutical option where there is significant clinical need in the context of poor prognosis. The two drug

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	options already available are often poorly tolerated due to side-effects, so this could be an option for those patients where other drug options have been exhausted. The trial data supports the option of the novel drug been used in combination with nintedanib to further slow disease progression. The trial data also suggest a reduction in hospitalisation, mortality and an increased to time of 1st exacerbation particularly in the context of progressive pulmonary fibrosis, which has both patient and economic benefits. There is no requirement for regular blood monitoring for this medication which is different to current anti fibrotic treatments which both require such monitoring. For this requirement to be removed has benefits for both the patient and the wider ILD service and NHS. For patients currently taking nintedanib or Pirfenidone, blood tests are required every month for the 1st 6 months, thereafter blood tests are required every 3 months if there blood results are stable.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	Who will provide an additional drug option therefore increasing complexity but for those services already providing anti fibrotic drug options this will be minimal as the drug is an oral preparation that does not require any monitoring.

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Decisions to discontinue this medication will be similar to decisions made to discontinue for other anti fibrotic agents namely patient preference and lack of efficacy
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	There is suggestion from the trial data FIBRONEER, in particular this study that relate to progressive pulmonary fibrosis that suggests a mortality benefit, reduction hospitalisation and delay until 1st hospitalisation. If borne out in clinical practice these factors will have an influence on the calculation of quality adjusted life year.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The drug is a novel anti fibrotic agent that is significantly different to other current treatment options for these disorders. To large scale phase 3 clinical trials have offered evidence to support its use in patients with both idiopathic pulmonary fibrosis and progressive pulmonary fibrosis either as a stand-alone therapy, and therefore a potential role for those who are intolerant of other options, or in combination with nintedanib. As a novel stand-alone therapy it offers an additional pharmaceutical option to those where Pirfenidone and nintedanib are not tolerated, therefore addressing an unmet need within this patient group.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side-effect profile of this medication is similar to nintedanib which is specialist centres who currently prescribe this medication are familiar with offering support and guidance.
20. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trials, in particularly the inclusion exclusion criteria, fairly reflect clinical practice. This is evidenced by the patient characteristics of those enrolled in the study which are a fair reflection of real world experience.

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There is an ongoing open label extension FIBRONEER-ON which will provide further insight into the long term use of this medication. The primary outcome of the trials was that of change in forced vital capacity which is the standard primary outcome for similar clinical trials making this study comparable to others. The secondary outcomes, which included time to 1st exacerbation, hospitalisation and mortality are clinically relevant and important to patients. The use of a quality of life questionnaire ensured that the impact of the medication be at beneficial or otherwise was considered.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance [TA504 (pirfenidone) and TA379, TA747 and TA864 (nintedanib)]?	No
23. How do data on real-world experience compare with the trial data?	There is limited real world experience with this novel treatment, the open label extension outcome is awaited.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	Those that do not have easy access to specialist ILD centres may be disadvantaged in terms of their access to novel treatments but this is beyond the scope of this review.

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

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Click or tap here to enter text.

Click or tap here to enter text.

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Single Technology Appraisal

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis [ID6446]

Clinical expert statement

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Part 1: Treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Philip Molyneaux
2. Name of organisation	Imperial College London
3. Job title or position	Professor of Interstitial Lung disease
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis? ☐ A specialist in the clinical evidence base for idiopathic pulmonary fibrosis or progressive pulmonary fibrosis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for idiopathic pulmonary fibrosis or progressive pulmonary fibrosis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Slow disease progression
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Slowing of decline in FVC by >50mls per year
10. In your view, is there an unmet need for patients and healthcare professionals in idiopathic pulmonary fibrosis or progressive pulmonary fibrosis?	Yes, current therapies are poorly tolerated, with a third of patients discontinuing due to side effects within a year and a large proportion unable to tolerate the effective target dose. Even on existing therapy the disease continues to progress and the addition of Nerandomilast on top of either of the current agents slows progression further.
11. How is idiopathic pulmonary fibrosis or progressive pulmonary fibrosis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The treatment for IPF is antifibrotic therapy, either Nintedanib or Pirfenidone (NICE technology appraisals 379, 864 and 504). For progressive pulmonary fibrosis (PPF) NICE technology appraisal 747 recommends nintedanib. These recommendations are in line with international consensus statements and guidelines (Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline, doi: 10.1164/rccm.202202-0399ST.) The care pathway is well defined and there is good agreement on this management pathway between professionals across the NHS. The technology would not impact the care pathway as such as patients but would provide another therapeutic option for clinicians and patients.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The drug could be used as monotherapy or as a combination with either pirfenidone or Nintedanib. This should be used in specialist care and prescribed by centres experienced in using antifibrotic therapy. Specialist nursing and pharmacy support are required.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. The data suggests this drug will be better tolerated and therefore patients will be able to maintain therapy longer. In addition, it's use in combination in patients who tolerate existing antifibrotics has been shown to incrementally slow lung function decline providing additional benefit. We know that FVC decline predicts mortality in pulmonary fibrosis so slowing this decline should increase length of life. Indeed in the PPF trial there was a significant survival benefit and in the IPF trial there was a numerical improvement. The first time we have seen such data in a clinical trial setting for pulmonary fibrosis. Quality of life will hopefully be maintained longer if patients are able to tolerate and maintain therapy. We know as lung function declines quality of life deteriorates and the rate of additional supportive therapy, such as oxygen therapy increases.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Easier. There is no need for routine blood monitoring (as is required with both Nintedanib and Pirfenidone), removing significant burden to patients and health care. A third of patients are currently on no therapy, and a large proportion of these patients choose not to accept treatment with either Nintedanib of Pirfenidone due to potential side effects.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	This therapy requires no monitoring of bloods, unlike the current therapies, so would be more easily managed and require less monitoring visits.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, this agent targets pulmonary fibrosis via both antifibrotic and immunomodulatory properties. It also preferentially targets the lungs via the PDE4b receptor.

• Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	It would be the first antifibrotic we could use as a combination therapy, providing incremental benefit to patients.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The drug appears well tolerated in the trial population with very low discontinuation rates.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, the patient population included reflects that seen in UK clinical practice from both a demographic and treatment perspective. The primary end point in both the IPF and PPF study was rate of decline in lung function (Forced vital capacity (FVC)) over 52 weeks. Nerandomilast significantly reduced the rate of FVC decline compared to standard of care in both patients with IPF and PPF. The effect was consistent across all subgroups of patients receiving either of the existing antifibrotic therapies or no therapy. FVC decline is widely accepted as the primary surrogate for mortality in IPF trials and is consistently associated with subsequent mortality in cohort studies. In the FIBRONEER-ILD trial of patients with PPF there was a 49% reduction in mortality. In the FIBRONEER-IPF study of patients with IPF the mortality signal was numerically encouraging but did not reach significance, likely due to lower event rates. I am not aware of any new adverse event data.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE	No

technology appraisal guidance [TA504 (pirfenidone) and TA379, TA747 and TA864 (nintedanib)]?	
23. How do data on real-world experience compare with the trial data?	There is no real-world experience data available.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	I do not know of any potential equality issues.

Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is currently a significant unmet need for effective and well tolerated patients with IPF and PPF

Nerandomolast is well tolerated and slows lung function decline in patients with IPF and PPF

It can be used a single agent or combined with existing antifibrotic therapy

In PPF it is the first drug to demonstrate a mortality benefit for patients

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Single Technology Appraisal

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis [ID6446]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis or caring for a patient with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on the **date specified in the accompanying email.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Patient expert statement

Part 1: Living with this condition or caring for a patient with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis

Table 1 About you, idiopathic pulmonary fibrosis or progressive pulmonary fibrosis, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☐ A patient with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Action for Pulmonary Fibrosis
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience

	☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Family experience of IPF, working in PF space for 3 years working closely with those affected, 2 surveys with over 2500 lived experience inputs, NHSE CRG Specialised Respiratory Member ☒ I have not completed part 2 of the statement
6. What is your experience of living with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis? **If you are a carer for someone with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for idiopathic pulmonary fibrosis or progressive pulmonary fibrosis on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for idiopathic pulmonary fibrosis or progressive pulmonary fibrosis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of nerandomilast over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does nerandomilast help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of nerandomilast over current treatments on the NHS please describe these. For example, are there any risks with nerandomilast? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from nerandomilast or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering idiopathic pulmonary fibrosis or progressive pulmonary fibrosis and nerandomilast? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

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External Assessment Group (EAG) Report

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis [ID6446]

Produced by Aberdeen HTA Group

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MI and MB reviewed and critiqued the clinical effectiveness evidence presented in the company submission; DA and JS checked and critiqued the statistical analyses presented in the company submission; MM and DB reviewed and critiqued the cost-effectiveness evidence and economic model presented in the company submission; PM checked and critiqued the company's search strategies; VK provided clinical guidance and comments on the draft report. DB coordinated all aspects of this appraisal. All authors contributed to the writing of this report and approved its final version.

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List of Abbreviations

Abbreviation	Definition
3L	Third line
AE	Adverse event
AESI	Adverse event of special interest
AF	Antifibrotic
APF	Action for Pulmonary Fibrosis
bid	Twice a day
BSC	Best supportive care
CI	Confidence interval
CPI	Composite Physiologic Index
CTCAE	Common Terminology Criteria for Adverse Events
DBL1	Database lock 1
DBL2	Database lock 2
EAG	Evidence Assessment Group
DILI	Drug-induced liver injury
DL_{CO}	Diffusing capacity of the lungs for carbon monoxide
FAS	Full analysis set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GAP	Gender, Age, Physiology
HCRU	Healthcare resource use
HR	Hazard ratio
HRCT	High-resolution computed tomography
HRQL	Health-related quality of life
ILD	Interstitial lung disease
IPD	Individual patient-level data
IPF	Idiopathic pulmonary fibrosis
IPTW	Inverse probability of treatment weighting
ITC	Indirect treatment comparison
L-PF	Living with Pulmonary Fibrosis questionnaire
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NMA	Network meta-analysis
OR	Odds ratio
OS	Overall survival
PDE4B	Phosphodiesterase 4B
PAS	Patient Access Scheme

Abbreviation	Definition
PF-ILD	Progressive fibrosing interstitial lung disease
PPF	Progressive pulmonary fibrosis
PT	Preferred term
RCT	Randomised controlled trial
RWD	Real-world data
RWE	Real-world evidence
SARD-ILD	Systemic-autoimmune-rheumatic disease interstitial lung disease
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TAs	Technology appraisals
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TS	Treated Set
TSD	Technical support document
TTD	Time to treatment discontinuation
UIP	Usual interstitial pneumonia

Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of EAG's key issues

The focus of the submission received from Boehringer Ingelheim is nerandomilast 18mg for the treatment of adults with idiopathic pulmonary fibrosis (IPF) or progressive pulmonary fibrosis (PPF). The company proposed nerandomilast 18mg as monotherapy used concomitantly with standard of care.

The company's main clinical effectiveness evidence for nerandomilast is obtained from two Phase 3, randomised, double-blind, placebo-controlled trials: FIBRONEER-IPF (NCT05231069) for people with IPF and FIBRONEER-ILD (NCT05321082) for people with PPF. In this Company Submission (CS), the FIBRONEER-IPF and FIBRONEER-ILD trial data are presented only for the subpopulation with 'no antifibrotic (AF) background therapy', which aligns with the intended monotherapy use of nerandomilast and with the company's economic model.

Table 1 Summary of key issues

ID 6446	Summary of issue	Impact on results	Report sections
1	The company have not considered competing risks for clinical outcomes	Unknown	3.3.1
2	The indirect treatment comparisons do not show statistically significant treatment benefits for nerandomilast vs. comparators	Potentially Large	3.5 and 4.2.5
3	Uncertainty regarding the continued duration of treatment benefit after treatment discontinuation	Potentially Large	4.2.5
4	Most appropriate sources of relative treatment benefit for the economic model for pirfenidone in IPF	Moderate – Large for PFN (IPF)	4.2.5
5	Company apply stopping rule to all active comparator, but EAG note there is not a stopping rule for NDB in NICE guidance for PPF.	Large – for comparisons vs. NDB for PPF	4.2.5
6	The company assumes monotherapies for all active treatments, no treatment sequencing	Unknown, potentially large	4.2.5

The company has submitted a Markov cohort model for the assessment of Nerandomilast 18mg vs. BSC, Nintedanib and Pirfenidone for IPF and for the assessment of Nerandomilast 18mg. vs BSC and Nintedanib for PPF. The model assumes all active treatments are used as monotherapy. The main drivers of incremental costs in the model are the treatment acquisition costs for nerandomilast, nintedanib and pirfenidone respectively. The main drivers of QALY gains are associated with modelled mortality benefits for nerandomilast 18mg vs. comparators. There are additionally some key areas of uncertainty that are not accounted for in

the economic modelling which may have an important impact on the ICER. These primarily relate to treatment sequencing, and it has not been possible for the EAG to fully explore a plausible ICER including treatment sequencing due to a lack of available data for 2nd line AF treatment. The EAG considers the bias, on balance, to be in favour of nerandomilast due to adding additional treatment acquisition costs of further lines of treatment post discontinuation in the pathway for a world with compared to a world without nerandomilast. The additional QALY gains of subsequent lines of treatment are uncertain, but it is plausible to assume that a second line of treatment in a group of patients who have already experienced disease deterioration on an AF therapy would not be as effective as the treatments use in a broader cohort (i.e. those progressing on nerandomilast are potentially a harder to treat group, hence likely to have lower QALY gains for the additional costs incurred of further treatment lines post discontinuation.

There is also an issue of unresolved uncertainty surrounding the potential stopping rule for nintedanib for PFN, which has been included in the model, but is not explicitly recommended in the relevant NICE guidance. This likely biases against nerandomilast. The kay differences between the company and EAG preferred base case ICERs, which it has been possible for the EAG to explore in the model are as follows:

2 The company prefers to assume equivalence between all active AF treatments in terms of health state transition probabilities, whereas the EAG prefers to use data from the NMR where available, and from the NMA for pirfenidone for IPF.

3 The company assumes equivalence between PFN and NDB for several clinical effectiveness parameters whereas the EAG prefers to use the available data from the Bayesian NMA.

4 The company prefers to apply an assumption of continued treatment effectiveness following discontinuation, based on time since treatment initiation, whereas the EAG prefer to assume treatment effectiveness is lost in the cycle following discontinuation. The EAG would welcome

exploration of additional approaches to model reducing treatment effect for the full cohort.

5 The EAG prefers to update some adverse event, cost and utility parameters in the model, but these have a comparatively minor impact on the ICER.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing life year gains for nerandomilast 18mg vs. comparators for both IPF and PPF.

Overall, the technology is modelled to affect costs by:

- Increasing treatment acquisition costs for Nerandomilast due to a higher treatment acquisition cost and longer time on treatment compared to other active treatment comparators, particularly for IPF.

The modelling assumptions that have the greatest effect on the ICER are:

- Mortality assumptions
- Magnitude of clinical benefit included in the economic model
- Continued treatment effect following discontinuation.

1.3 EAG's key issues

Overall, the company's decision problem aligns with the NICE final scope. The EAG's key issues for this assessment are summarised below.

Issue 1 non-consideration of competing risks for clinical outcomes

Report section	Section 3.3.1 of the EAG report
Description of issue and why the EAG has identified it as important	Use of composite endpoint and Cox regression analysis of the trial secondary outcome. The company used Cox regression to analyse important endpoints, including death and other non-fatal outcomes. This assumes that the risk of the non-fatal event for those who died is the same as for those who remain under observation. This may create an unquantifiable bias in the estimate of the non-fatal event risk.
What alternative approach has the EAG suggested?	The EAG would prefer a competing risk analysis approach for non-fatal outcomes.
What is the expected effect on the cost-effectiveness estimates?	It is not possible to quantify the direction and magnitude of this effect without carrying out a competing risk analysis, particularly for non-fatal outcomes. This impacts on acute exacerbation rates in the economic model. It is plausible that failure to account for competing risks in the economic model could introduce bias in the cost-effectiveness estimates. Due to the way in which the company has modelled acute exacerbations, the magnitude of bias is likely to be small.
Could any additional evidence or analyses be provided to resolve this key issue?	This issue concerns the analytical approach and the EAG's view that the company has not adequately considered the potential biases arising from their chosen approach. The company could have presented results from competing risks models and integrated these findings into the cost-effectiveness modelling.

Issue 2 No significant effects in most comparisons

Report section	Section 3.5.3 of the EAG report
Description of issue and why the EAG has identified it as important	Non-significance of the main effects of nerandomilast vs comparators. The ITC analyses did not show any significant difference between nerandomilast and nintedanib and pirfenidone in treatment effectiveness outcomes. Also, a substantial number of the computed credible intervals were very wide. Both issues reflect substantial uncertainty in the clinical effectiveness of nerandomilast against comparators.
What alternative approach has the EAG suggested?	This issue highlights that the EAG is unable to confirm whether nerandomilast provides any clinical advantage over the comparators.
What is the expected effect on the cost-effectiveness estimates?	The implication is that uncertainty surrounding the base case ICER is extremely high. The EAG prefers to include treatment effect estimates in the economic model, sampling the uncertainty in the probabilistic analysis. The EAG also provides the results of scenario analyses assuming equivalence in treatment effectiveness outcomes.
Could any additional evidence or analyses be provided to resolve this key issue?	As this is essentially subject to the evidence available, this issue may not be resolvable now.

Issue 3 Uncertainty regarding the continued duration of treatment benefit after treatment discontinuation

Report section	Section 4.2.5
Description of issue and why the EAG has identified it as important	The company preferred approach assumes that there is a continued treatment effect of active treatments following treatment discontinuation, based on time since treatment initiation. This is applied for one year after the follow-up period of the FIBRONEER trials. The most appropriate assumptions about continuing treatment effects after discontinuation have an important impact on the ICER.
What alternative approach has the EAG suggested?	The EAG would consider it more appropriate to assign BSC transition probabilities immediately following discontinuation of active treatments, especially given the short half-life of the active treatments. The EAG accepts that there may also be treatment waning whilst on active treatments and this has not been explored. One alternative approach could be to apply treatment waning to the whole cohort, reflecting the average treatment discontinuation curves.
What is the expected effect on the cost-effectiveness estimates?	The EAG's preferred approach substantially increases the ICER for both IPF and PPF cost-effectiveness models.
Could any additional evidence or analyses be provided to resolve this key issue?	The EAG would welcome further exploration of different approaches to treatment effect waning in the economic model that align with discontinuation and / or reflect converging hazards for the full cohort.

Issue 4 Most appropriate sources of relative treatment benefit for the economic model for pirfenidone in IPF

Report section	Section 4.2.5
Description of issue and why the EAG has identified it as important	The company preferred base case applies an assumption of equivalence in mortality and acute exacerbation for nintedanib and pirfenidone for IPF. This is an important issue because it impacts on the ICER for Nerandomilast 18mg vs. Pirfenidone for the IPF model.
What alternative approach has the EAG suggested?	The EAG prefers to make use of the best available data, using the IPD pooled analysis NMR for comparisons of nerandomilast vs. nintedanib. The EAG then prefers to prioritise treatment effect estimates from the NMA for comparisons between Nerandomilast 18mg vs. Pirfenidone. The company have raised concerns about the limitations of the NMA due to lack of population adjustments potentially leading to confounding of results. However, the EAG consider this less biased than assuming equivalence, particularly given substantial uncertainty as illustrated from wide confidence intervals. The EAG prefers that this uncertainty is accounted for within the probabilistic sensitivity analyses.
What is the expected effect on the cost-effectiveness estimates?	The impact of applying the EAG's preferred assumptions is an increase in the ICER for nerandomilast 18mg vs. pirfenidone for IPF.
Could any additional evidence or analyses be provided to resolve this key issue?	The EAG is satisfied that all the relevant information is available from the company's NMA report to make an informed judgement on the most appropriate base case assumptions to apply.

Issue 5 Stopping rules

Report section	Section 4.2.5
Description of issue and why the EAG has identified it as important	The company base case analysis applies stopping rules for all active treatment comparators in both the IPF and PPF economic models. Stopping rules have an important impact on costs in the economic model.
What alternative approach has the EAG suggested?	The EAG considers the company's preferred base case analysis to be appropriate but conservative, especially for PPF. The EAG notes that a stopping rule is not explicitly recommended in NICE guidance for nintedanib for PPF. Whilst the guidance assumes that clinicians will stop treatment when it is no longer effective, it is unclear how this is defined, at what time points it applies, or how closely it aligns with the defined stopping rule in the company's economic model (stopping treatment immediately upon a FVC % predicted progression >10%).
What is the expected effect on the cost-effectiveness estimates?	The impact of applying an alternative assumption of removing the stopping rule for nintedanib for PPF substantially reduces the ICER for nerandomilast vs. nintedanib for PPF.
Could any additional evidence or analyses be provided to resolve this key issue?	The EAG would welcome further clinical expert viewpoints on how stopping rules are implemented currently in UK clinical practice for active AF treatments, especially nintedanib for PPF.

Issue 6 Treatment sequencing

Report section	Section 4.2.5
Description of issue and why the EAG has identified it as important	The company base case analysis compares active treatments as monotherapies, with no potential to move to second line active AF treatments following a loss of treatment effectiveness. This creates a bias of uncertain direction and magnitude for cost-effectiveness.
What alternative approach has the EAG suggested?	Whilst the EAG are satisfied that initiation of a second AF treatment was rare in the company's FIBRONEER trials, the EAG are of the view that if multiple treatments are available to clinicians, these would be used in UK clinical practice in sequence. This uncertainty poses a substantial modelling challenge as there is insufficient evidence to support robust evaluation of effectiveness of comparators used as second line treatments.
What is the expected effect on the cost-effectiveness estimates?	The impact on the ICER of a modelling approach that may not reflect UK clinical practice in terms of treatment sequencing is unclear. Second line treatments would add additional treatment acquisition costs to the pathway, especially for nerandomilast, but the magnitude of QALY gains is unknown.
Could any additional evidence or analyses be provided to resolve this key issue?	It is unlikely to be possible to adequately address this uncertainty in the economic modelling, however further clarification from a range of UK clinical experts regarding how treatments would be used in sequence in clinical practice would be beneficial. Perhaps experience of using pirfenidone and nintedanib for IPF might provide useful insight.

1.4 Secondary issues identified by the EAG

There are minor differences between company and EAG preferred application of utilities in the economic model which only have a minor impact on the ICER. In brief, the company applies a disutility for liver function testing, but the EAG considers the

value to be uncertain and prefers to exclude it from the base case analysis. The EAG also prefers to apply a longer period of disutility for acute exacerbations in the model (30 days as opposed to 10 days in the company preferred base case). The EAG has also made some minor updates to the NHS reference costs and adverse events in the model. All of these issues only have a minor impact on the ICER.

1.5 Company's modelling errors identified by the EAG

The EAG and company have both identified several data input errors with respect to clinical effectiveness parameters used in the model, and discrepancies between the full statistical analysis reports (NMR and NMA) compared to data entered in the economic model. The company provided an addendum to their submission addressing several of these issues, but the EAG has some remaining concerns about discrepancies between the addendum and the submitted statistical analyses reports. Where possible, the EAG has corrected issues identified and would welcome further clarification from the company confirming the correct input parameters.

The EAG identified several minor data parameter input errors and discrepancies between the company's economic model and submitted reports with respect to NHS reference costs applied to resource use and adverse event disutilities. These only had a minor impact on the ICER.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2 EAG preferred assumptions and ICER pairwise Nerandomilast vs. comparator (IPF)

Comparator	Incremental Costs (Nera 18mg vs. comp) (£)	Incremental QALYs (Nera 18mg vs. comp)	ICER (Nera 18mg vs. comp)
Company base case analysis			
BSC	[redacted]	1.14	[redacted]
NDB	[redacted]	0.93	[redacted]
PFN	[redacted]	0.93	[redacted]

Comparator	Incremental Costs (Nera 18mg vs. comp) (£)	Incremental QALYs (Nera 18mg vs. comp)	ICER (Nera 18mg vs. comp)
Scenario 1 – Apply rate ratio from NMR for NDB health state transition probabilities (Rate ratio: Nera 18mg vs. NDB: [redacted])			
BSC	[redacted]	1.14	[redacted]
NDB	[redacted]	0.92	[redacted]
PFN	[redacted]	0.93	[redacted]
Scenario 2 – As per scenario 1, plus apply OR from NMA for PFN health state transition probabilities (Odds ratio: Nera 18mg vs. PFN: [redacted])[A]			
BSC	[redacted]	1.14	[redacted]
NDB	[redacted]	0.92	[redacted]
PFN	[redacted]	0.92	[redacted]
Scenario 3 – Apply HR of mortality from NMA; Nerandomilast vs. Pirfenidone ([redacted])			
BSC	[redacted]	1.14	[redacted]
NDB	[redacted]	0.93	[redacted]
PFN	[redacted]	0.74	[redacted]
Scenario 4 – Apply OR from NMA for calculating risk of acute exacerbations per cycle: Nerandomilast 18mg vs. PFN ([redacted])			
BSC	[redacted]	1.14	[redacted]
NDB	[redacted]	0.93	[redacted]
PFN	[redacted]	0.93	[redacted]
Scenario 5 – Apply Treatment discontinuation HR from NMR for nerandomilast 18mg vs. NDB ([redacted])[B]			
BSC	[redacted]	1.14	[redacted]
NDB	[redacted]	0.93	[redacted]
PFN	[redacted]	0.93	[redacted]
Scenario 6 – As per scenario 5 + Apply Treatment discontinuation OR from NMA for nerandomilast 18mg vs. PFN ([redacted])[B]			
BSC	[redacted]	1.14	[redacted]
NDB	[redacted]	0.93	[redacted]
PFN	[redacted]	0.93	[redacted]
Scenario 7 – remove company's continued treatment benefit post discontinuation assumption			
BSC	[redacted]	0.86	[redacted]
NDB	[redacted]	0.73	[redacted]
PFN	[redacted]	0.73	[redacted]

Comparator	Incremental Costs (Nera 18mg vs. comp) (£)	Incremental QALYs (Nera 18mg vs. comp)	ICER (Nera 18mg vs. comp)
Scenario 8 – Apply EAG correction to application of acute exacerbation disutilities			
BSC	[redacted]	1.14	[redacted]
NDB	[redacted]	0.93	[redacted]
PFN	[redacted]	0.93	[redacted]
Scenario 9 (remove liver function test disutility)			
BSC	[redacted]	1.14	[redacted]
NDB	[redacted]	0.92	[redacted]
PFN	[redacted]	0.92	[redacted]
Scenario 10 - Apply EAG preferred AE assumptions (include GI perforation, rescale utility values and apply corrected NHS reference costs)			
BSC	[redacted]	1.14	[redacted]
NDB	[redacted]	0.93	[redacted]
PFN	[redacted]	0.93	[redacted]
Scenario 11 – Apply corrected NHS reference costs for Physiotherapy and Occupational Therapy visits			
BSC	[redacted]	1.14	[redacted]
NDB	[redacted]	0.93	[redacted]
PFN	[redacted]	0.93	[redacted]
EAG preferred base case analysis - deterministic (Scenarios 1-11 combined)			
BSC	[redacted]	0.86	[redacted]
NDB	[redacted]	0.72	[redacted]
PFN	[redacted]	0.57	[redacted]
EAG preferred base case analysis - probabilistic			
BSC	[redacted]	0.82	[redacted]
NDB	[redacted]	0.73	[redacted]
PFN	[redacted]	0.55	[redacted]

Table 3 EAG preferred assumptions and ICER pairwise Nerandomilast vs. comparator (PPF)

Comparator (Nera 18mg vs.)	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
Company base case analysis			
BSC	[redacted]	0.8	[redacted]
NDB	[redacted]	0.47	[redacted]
Scenario 1 – Apply rate ratio from NMR for NDB health state transition probabilities (Rate ratio: Nera 18mg vs. NDB: [redacted])			
BSC	[redacted]	0.8	[redacted]
NDB	[redacted]	0.46	[redacted]
Scenario 2 – Apply Treatment discontinuation HR from NMR for nerandomilast 18mg vs. NDB ([redacted])			
BSC	[redacted]	0.8	[redacted]
NDB	[redacted]	0.47	[redacted]
Scenario 3 – remove company's continued treatment benefit post discontinuation assumption			
BSC	[redacted]	0.51	[redacted]
NDB	[redacted]	0.33	[redacted]
Scenario 4 – Apply EAG correction to application of acute exacerbation disutilities			
BSC	[redacted]	0.8	[redacted]
NDB	[redacted]	0.47	[redacted]
Scenario 5 (remove liver function test disutility)			
BSC	[redacted]	0.8	[redacted]
NDB	[redacted]	0.46	[redacted]
Scenario 6 - Apply EAG preferred AE assumptions (include GI perforation, rescale utility values and apply corrected NHS reference costs)			
BSC	[redacted]	0.8	[redacted]
NDB	[redacted]	0.47	[redacted]
Scenario 7 – Apply corrected NHS reference costs for Physiotherapy and Occupational Therapy visits			
BSC	[redacted]	0.8	[redacted]
NDB	[redacted]	0.47	[redacted]

Comparator (Nera 18mg vs.)	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
EAG preferred base case analysis - deterministic (Scenarios 1-7 combined)			
BSC	[redacted]	0.51	[redacted]
NDB	[redacted]	0.31	[redacted]
EAG preferred base case analysis - probabilistic			
BSC	[redacted]	0.5	[redacted]
NDB	[redacted]	0.31	[redacted]

1.7 Outline of confidential comparator or subsequent treatment prices

A confidential appendix is provided alongside the EAG report detailing the results of all cost-effectiveness analyses provided by the company and EAG with confidential comparator prices for nintedanib applied. Further details are available in Section 5.4 of the EAG report.

2 Background

This report critiques the submission received from Boehringer Ingelheim for nerandomilast (brandname: Jascayed®) for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis.

The company's description of the health condition in terms of prevalence, symptoms and complications appears accurate and in line with the decision problem.

2.1 Critique of the company's description of underlying health problem

The company submission (CS) describes idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF) as chronic, progressive forms of interstitial lung disease (ILD) characterised by declining lung function that is associated with high morbidity and early mortality.[1, 2] In both IPF and PPF, abnormal inflammatory and fibrotic responses occur during the repair of lung tissue injury. This process leads to irreversible pulmonary tissue scarring (pulmonary fibrosis), making the lungs stiff and less able to function properly.[3, 4] IPF is a specific progressive fibrosing form of interstitial lung disease (ILD) with no identifiable aetiology that typically occurs in older adults, whereas PPF describes a broader progressive fibrosing phenotype that can develop in a variety of ILDs of known or unknown aetiology, excluding IPF.[2, 5, 6]

Declines in forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLco) are commonly used as a marker of disease progression in pulmonary fibrosis, with acute exacerbations associated with a more rapid deterioration in lung function.[7, 8] Current therapies aim to slow disease progression, as indicated by a reduced rate of decline in lung function.[9] However, they do not reverse established fibrosis or halt its progression, and treatment options for IPF and PPF remain limited.[9]

2.2 Critique of the company's overview of current service provision

The CS cites the 2017 NICE guideline CG163 for the management of IPF in adults[10] and technology appraisals for treatments for IPF. There are currently two antifibrotic (AF) therapies approved and recommended for the treatment of IPF, namely:

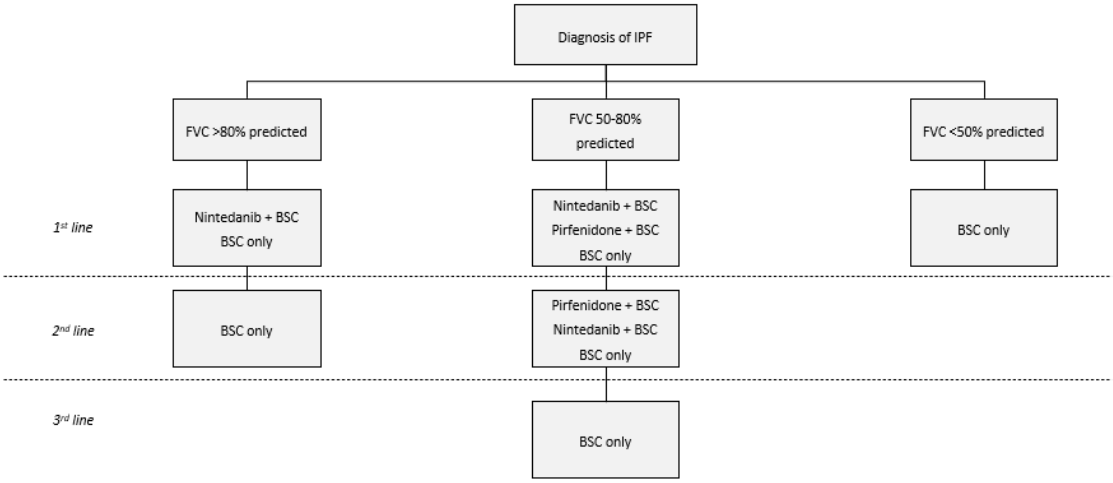
- Nintedanib for people with a FVC between 50% and 80% predicted [TA379][11] or >80% predicted [TA864][12]

- Pirfenidone for people with a FVC between 50% and 80% predicted [TA504][13]

There are currently no UK-specific clinical guidelines for managing PPF (Section 1.3.4.2 of the CS), and the only treatment recommended by NICE is nintedanib [TA747][14] In patients who develop PPF, immunomodulatory treatments may have been used earlier to treat the underlying ILD, depending on disease type. Immunosuppressive therapy may then be continued or tapered, regardless of whether nintedanib is initiated.[14]

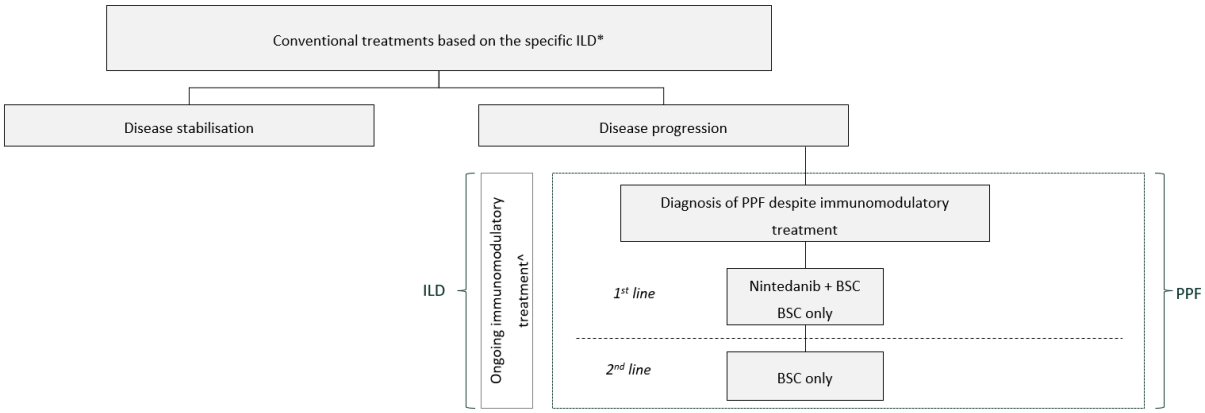
Best supportive care (BSC) is routinely offered to all patients with IPF or PPF. The company provides a description of the current clinical pathway in Section B.1.3.4 of the CS. An overview of the treatment pathway for patients with IPF and PPF are presented as Figure 3 and Figure 4 of the CS, respectively, reproduced as Figures 1 and 2 below.

The anticipated place for nerandomilast is presented in Figure 4 and 5 of the CS and is reproduced as Figure 3 and 4. Nerandomilast is intended as a monotherapy. It may be used concomitantly with BSC and, for patients with PPF, alongside immunomodulatory treatment for the underlying ILD diagnoses.



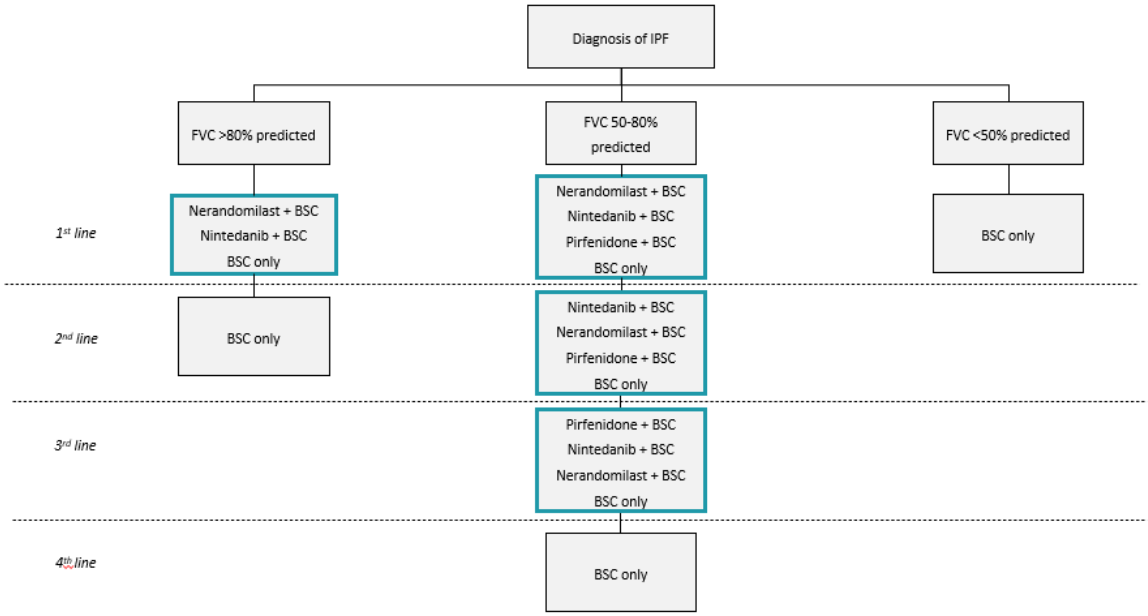
Key: BSC, best supportive care; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.
Source: Adapted from NICE (CG163);[10] NICE (TA864);[12] NICE (TA379);[11] NICE (TA504).[13]

Figure 1 Care pathway for IPF in England and Wales [Reproduced from Figure 3 of the CS]



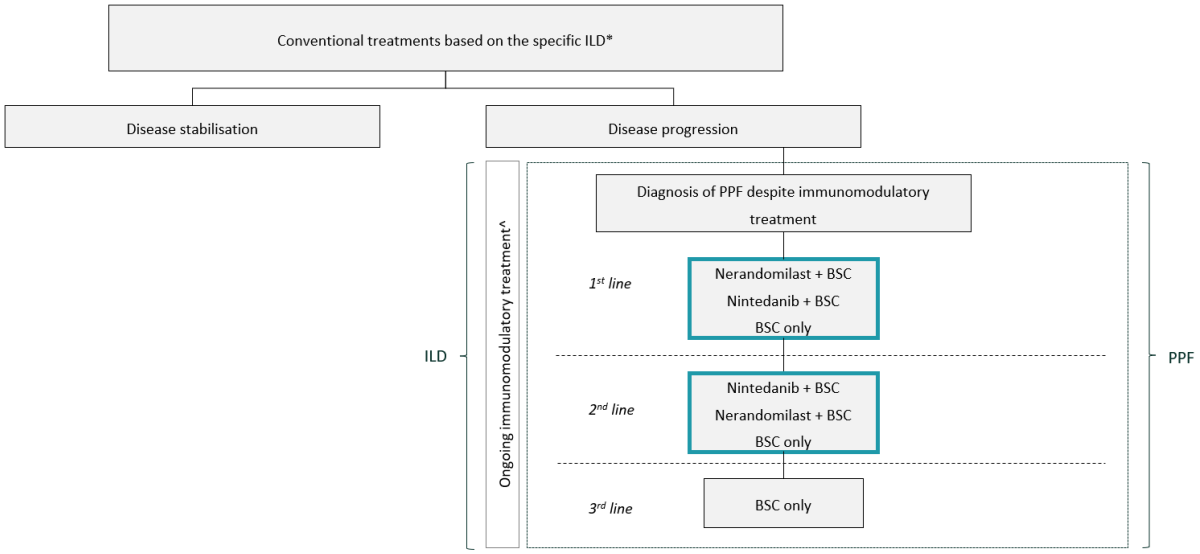
Key: BSC, best supportive care; ILD, interstitial lung disease; PPF, progressive pulmonary fibrosis.
Notes: *Including, but not limited to, immunosuppressants (mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate), corticosteroids, infliximab or rituximab; ^some but not all patients may continue to receive ongoing immunomodulatory treatment for underlying ILD.
Source: adapted from NICE (TA747).[14]

Figure 2 Care pathway for PPF in England and Wales [Reproduced from Figure 4 of the CS]



Key: BSC, best supportive care; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.

Figure 3 Proposed positioning of nerandomilast in the care pathway for IPF [Reproduced from Figure 5 of the CS]



Key: BSC, best supportive care; ILD, interstitial lung disease; PPF, progressive pulmonary fibrosis.
Notes: *Including, but not limited to immunosuppressants (mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate), corticosteroids, infliximab or rituximab; ^some but not all patients may continue to receive ongoing immunomodulatory treatment for underlying ILD.

Figure 4 Proposed positioning of nerandomilast in the care pathway for PPF [Reproduced from Figure 6 of the CS]

2.3 Critique of the company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 4 below. A critique of the adherence of the company's economic modelling to the NICE reference case is presented in Chapter 4.

Table 4 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with idiopathic pulmonary fibrosis or progressive pulmonary fibrosis	People with IPF or PPF	No difference.	The population described in the CS matches that described in the NICE final scope.
Intervention	Nerandomilast	Nerandomilast monotherapy (18 mg bid)	Focused to the intended use (monotherapy) and recommended dosing of nerandomilast (18 mg bid, in line with expected marketing authorisation). Results for nerandomilast monotherapy at the lower dose of 9 mg bid are also shown for reference in clinical data tables and figures, as this dose will be available for patients unable to tolerate the 18 mg bid dosing.	The EAG considers the intervention addressed by the company to be appropriate. The CS describes nerandomilast as an oral inhibitor of phosphodiesterase 4 (PDE4) with preferential inhibition of the PDE4B isoenzyme. It exerts both antifibrotic (AF) and immunomodulatory effects, as inhibition of PDE4B in the lung is expected to reduce the expression of pro-fibrotic growth factors and inflammatory cytokines. This reduces fibroblast proliferation and differentiation into myofibroblast, promoting fibroblast cell death and decreasing the synthesis, release and function of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				extracellular matrix (ECM) components.[15] Nerandomilast as monotherapy is indicated for the treatment of adult patients with IPF and the treatment of adult patients with PPF. The recommended dose is 18 mg twice daily (BID), with a possible reduction to 9 mg BID depending on patient tolerability.[15] The CS notes that a marketing authorisation application was submitted to the MHRA in [redacted]. The anticipated date of UK regulatory approval is [redacted] 2026.
Comparator(s)	Established clinical management without nerandomilast, including but not limited to: For idiopathic pulmonary fibrosis: • nintedanib	For IPF: • nintedanib • pirfenidone (in people who have a FVC of 50% to 80% predicted) • best supportive care	For PPF: Immunosuppressants, corticosteroids, infliximab and rituximab may be used to treat the underlying ILD but are not licensed for the treatment of PPF in the UK. Nintedanib is currently	The EAG clinical expert considered the comparators included in the company's decision problem to be appropriate.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• pirfenidone (in people who have a FVC of 50% to 80% predicted) • best supportive care For progressive pulmonary fibrosis: • nintedanib • immunosuppressants , such as methotrexate, azathioprine, cyclophosphamide or mycophenolate • corticosteroids • infliximab • rituximab • best supportive care	For PPF: • nintedanib • best supportive care	the only licensed treatment for PPF in the UK. Immunosuppressants, corticosteroids, infliximab and rituximab may be used alongside nintedanib in the current pathway of care and could also be used in this concomitant way with nerandomilast. Nerandomilast would not replace these treatments and, as such, they do not meet the definition of a comparator as per the NICE process and methods.	
Outcomes	The outcome measures to be considered include: • pulmonary function • physical function • exacerbation rate • hospitalisations	The outcome measures to be considered include: • pulmonary function • physical function • exacerbation rate • hospitalisations	While lung transplantation could be considered a marker for progression of lung disease, it is not a relevant outcome for this patient population. Patients whose pulmonary function declines to FVC <50% predicted may be considered for	Lung transplantation could have been considered a relevant outcome for the economic modelling, but there is limited evidence to populate model parameters with respect to transplantation. Therefore, any scenarios incorporating lung

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• lung transplantation • mortality • adverse effects of treatment • health-related quality of life	• mortality • adverse effects of treatment • health-related quality of life	lung transplantation, but internal estimates and the FIBRONEER trial programme suggest that a small proportion of patients with IPF or PPF ultimately undergo lung transplantation – around [redacted]%. This is supported by <5% lung transplantation referral rates captured in the BTS ILD Registry.[16]	transplantation would be highly uncertain.
Subgroups	If the evidence allows the following subgroups will be considered: • Idiopathic pulmonary fibrosis • Progressive pulmonary fibrosis • Disease severity defined by FVC	• IPF • PPF	No difference from the final NICE scope. Data for IPF and PPF are presented separately in Section 2.6 aligning to the FIBRONEER trial programme. Post hoc pooled IPF and PPF analyses are presented in Section 2.9. Pre-specified subgroup analyses based on baseline FVC % predicted ≤ and >70% for the FAS population are presented in Appendix C. Post-hoc subgroup analyses based on baseline FVC % predicted ≤ and >80% for the	As per scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			monotherapy population are under investigation.	
Special considerations including issues related to equity or equality	NA	NA	NA	NA
Key: bid, twice a day; BTS British Thoracic Society; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NICE, National Institute for Health and Care Excellence; PPF, progressive pulmonary fibrosis.				

3 Clinical effectiveness

This section presents a summary and critique of the clinical-effectiveness evidence included in the company's submission. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 to 3.3 provide a critique of the included studies and clinical-effectiveness analyses. Sections 3.4 to 3.5 critique any indirect comparisons presented by the company. Section 3.6 covers additional work done by the EAG.

3.1 Critique of the methods of review

Full details of the methods used by the company to identify and select the clinical evidence relevant to this appraisal are reported in Appendix B of the CS. The EAG's appraisal of the company's systematic literature review (SLR) methodology is summarised in Table 5.

Table 5 EAG's appraisal of the literature review methods presented in the CS

Review process EAG	EAG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details are provided in Appendix B of the CS. Searches were not restricted by any eligibility criteria, so all results were discovered and only those relevant to the scope were selected.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, and CENTRAL for primary research. Relevant conference proceedings, trial registers and HTA organisations were also searched. Bibliographies of recent SLRs were examined to identify relevant studies not captured by the literature searches. Full details are provided in Appendix B of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	The eligibility criteria outlined in Appendix B, Sections B.1.4.1.1 and B1.4.1.2 (Table 7) for IPF and Sections B.1.4.2.1 and B.1.4.2.2 (Table 8) are consistent with the decision problem outlined in the NICE final scope.

Review process EAG	EAG response	Comments
Was study selection conducted by two or more reviewers independently?	Yes	The company's clarification response reported that two reviewers working independently carried out the title and abstract screening and full text screening.
Was data extraction conducted by two or more reviewers independently?	Unclear	This information was not provided in the CS.
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	Appendix B, Section B.3, states that critical appraisal of FIBRONEER-IPF and FIBRONEER-ILD was conducted using the Cochrane Risk of Bias 2.0 checklist.
Was the risk of bias assessment conducted by two or more reviewers independently?	Partially	The company's clarification response reported that risk-of-bias assessment was conducted by one reviewer and verified against the original source(s) by a second reviewer.
Was identified evidence synthesised using appropriate methods?	Mostly	The company's approach of a Cox model for composite outcomes presents a risk of bias because of the inherent assumption that the risk of non-fatal outcomes among those that were censored at death remains the same as those remaining on the at-risk population.

The EAG conducted a quality assessment of the methods used by the company for the SLR of clinical evidence based on the Centre for Reviews and Dissemination (CRD) criteria. The results are presented in Table 6.

Table 6 Quality assessment of the company's systematic literature review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies that address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.2 Critique of the methods of the trials of the technology of interest

3.2.1 Included studies

The key clinical effectiveness evidence is presented in Section 2 of the CS. The company's main clinical evidence for nerandomilast is obtained from FIBRONEER-IPF (NCT05231069) for people with IPF and FIBRONEER-ILD (NCT05321082) for people with PPF. FIBRONEER-IPF and FIBRONEER-ILD are Phase 3, randomised, double-blind, placebo-controlled trials, evaluating nerandomilast versus placebo in adults with IPF and PPF, respectively. In this CS, the FIBRONEER-IPF and FIBRONEER-ILD trial data are presented only for the subpopulation with 'no antifibrotic (AF) background therapy', which aligns with the intended monotherapy use of nerandomilast. *The EAG has no major concerns about the design and conduct of this trial.*

The participant flow in the FIBRONEER-IPF and FIBRONEER-ILD studies is presented in Appendix B, Section B.2, Figure 11 of the CS. An overview of the study is presented in Table 4 of the CS, with an adapted version shown in Table 7 below.

The FIBRONEER-IPF study was conducted at 332 sites in 36 countries, and the FIBRONEER-ILD study at 403 sites in 44 countries, including the UK (see Appendix I).

In the FIBRONEER-IPF study, 1,177 patients with IPF were randomised 1:1:1 to receive nerandomilast 18 mg bid, nerandomilast 9 mg bid, or placebo, in addition to the patient's standard of care; of these 262 (22.3%) received monotherapy and comprised the 'no AF background therapy' cohort included in the current CS. In the FIBRONEER-ILD study, 1,178 patients with PPF were randomised similarly, in addition to the patient's standard of care, of whom 662 (51.2%) comprised the monotherapy 'no AF background therapy' cohort reported in this CS. Although the trials were not statistically powered to evaluate the 'no AF background therapy' cohort specifically, it was a pre-specified subgroup in both trials, with randomisation

stratified by the presence or absence of AF background therapy (AF vs. no AF). The CS also states that placebo monotherapy in both trials effectively represents BSC.

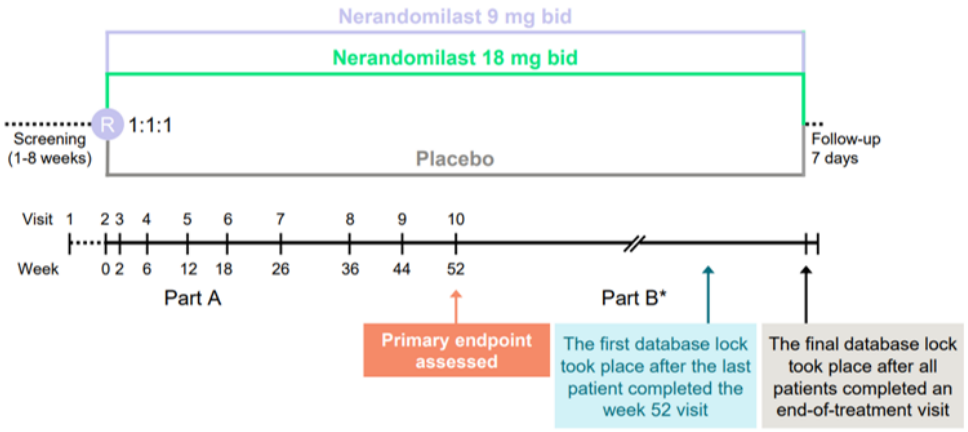
Table 7 Clinical effectiveness studies of technology of interest (Adapted from Table 4 of the CS)

	FIBRONEER-IPF (NCT05321069)	FIBRONEER-ILD (NCT05321082)
Role in this evaluation	Key source of clinical effectiveness;	Key source of clinical effectiveness;
Study type	Randomised, double-blind, placebo-controlled trial evaluating the efficacy and safety of nerandomilast (9 mg or 18 mg) over at least 52 weeks in patients with IPF.	Randomised, double-blind placebo-controlled trial evaluating the efficacy and safety of nerandomilast (9 mg or 18 mg) over at least 52 weeks in patients with PPF.
Patient group	Adults with IPF	Adults with PPF
Intervention	Nerandomilast (9 mg or 18 mg bid) + patients' standard of care treatment.	Nerandomilast (9 mg or 18 mg bid) + patients' standard of care treatment.
Comparator	Placebo (matching the nerandomilast tablets) + patients' standard of care treatment.	Placebo (matching the nerandomilast tablets) + patients' standard of care treatment.
Duration	At least 52 weeks	At least 52 weeks
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	NA	NA
Reported outcomes specified in the decision problem	**Pulmonary / physical function** • Absolute change from baseline in FVC (absolute change [ml] and change in % predicted) and DL_{CO} % predicted • Time to first occurrence of any of the components of the composite endpoint: acute IPF exacerbation, hospitalisation for respiratory cause or death • Time to absolute decline in FVC % predicted of > 10% /DL_{CO} % predicted of > 15%	

	• Absolute change from baseline in L-PF symptom scores • Use of supplemental oxygen **Exacerbation rate** • Time to first acute IPF exacerbation Hospitalisation rate • Time to first acute hospitalisation for respiratory cause **Mortality** • Time to death **Health-related quality of life** • EQ-5D VAS **Adverse effects of treatment**
Key: bid, twice a day; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; L-PF, Living with Pulmonary Fibrosis questionnaire; N/A, not applicable; PPF, progressive pulmonary fibrosis. **Notes:** Bolded outcomes are those used in the economic modelling. **Source:** Maher et al. 2025;[17] Richeldi et al. 2022;[18] Richeldi et al. 2025.[19]	

Participants received nerandomilast (9 mg or 18 mg bid) or matching placebo alongside standard-of-care treatment over at least 52 weeks. Thereafter, participants continued to receive randomised blinded treatment for a variable duration. An overview of the FIBRONEER trials study design is depicted in Figure 5 below.

The dose of interest in this CS is 18 mg bid, consistent with the UK marketing authorisation. While a reduced 9 mg bid dose is permitted for patients based on individual tolerability, the proportion of participants receiving this lower dose is not reported for either study, and this group does not exactly correspond to the 9 mg bid groups randomised in the trials. The CS notes that results for 9 mg bid are shown for reference only.



Key: bid, twice a day; CTR, clinical trial report.
Notes: *visits occurred every 12 weeks until the last patient completed 52 weeks of treatment.
Source: adapted from FIBRONEER-IPF CTR[20] and FIBRONEER-ILD CTR.[21]

Figure 5 Study design overview for FIBRONEER-IPF and FIBRONEER-ILD [Reproduced from Figure 7 of the CS]

Summaries of the baseline participant and disease characteristics of the FIBRONEER trials are presented in Tables 5 and 6 of the CS and reproduced as Tables 8 and 9 below.

In FIBRONEER-IPF, most randomised participants were male (76%). The mean (standard deviation [SD]) age was 70.4 (8.4) years. [redacted]. Baseline clinical characteristics were generally similar across the trial groups. The mean (SD) FVC was 82.2% (17.9) of the predicted value, and the mean (SD) DLco was 55.18% (18.3) of the predicted value. A total of [redacted] patients had not received prior AF treatment.

In FIBRONEER-ILD, approximately half of the participants were male (49.8%). The mean (SD) age was 66.2 (10.4) years, and [redacted]. Clinical characteristics were broadly comparable across treatment groups. Mean (SD) FVC was 71.1% (16.0) of predicted and mean (SD) DLco was 52.5% (16.7) of predicted. In total, [redacted] patients were treatment-naïve for AF.

Overall, although the ethnic composition differs from that of the UK, the EAG clinical advisor is of the opinion that the participants in the FIBRONEER studies are broadly representative of patients with IPF and PPF seen in NHS clinical practice.

The CS describes that quality and risk of bias assessment for RCT studies was undertaken using the revised Cochrane risk-of-bias (ROB2) tool (Appendix B, Section B.3, Table 16).

The EAG generally agrees with the company's quality assessment of the FIBRONEER studies and regards them as being of good methodological quality.

Table 8 Baseline characteristics of patients, FIBRONEER-IPF ('no AF background therapy' cohort) [Adapted from Table 5 of the clarification response; which was based on Table 5 of the CS]

Characteristic	Nera 18 mg bid N = 87	Nera 9 mg bid N = 88	Placebo N = 87	Total N = 262
Male sex, n (%)	68 (78.2)	63 (71.6)	68 (78.2)	199 (76.0)
Age, mean (SD), years	70.1 (8.8)	70.3 (8.4)	70.9 (8.2)	70.4 (8.4)
Weight, mean (SD), kg	71.86 (13.4)	73.41 (16.4)	74.4 (14.2)	73.23 (14.7)
Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Black/African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Multiple, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status, n (%)[a]				
Never smoked	29 (33.3)	25 (28.4)	23 (26.4)	77 (29.4)
Former smoker	56 (64.4)	60 (68.2)	61 (70.1)	177 (67.6)
Current smoker	2 (2.3)	3 (3.4)	3 (3.4)	8 (3.1)
Time since diagnosis of IPF, mean (SD), years	2.93 (3.1)	2.78 (2.5)	2.78 (3.2)	2.83 (2.9)
FVC				
Mean value (SD), mL	2761.4 (778.4)	2763.6 (739.3)	2833.3 (885.7)	2786 (800.9)
Mean % predicted (SD)	82.1 (18.7)	82.31 (15.7)	82.18 (19.5)	82.2 (17.9)
DL_{CO}, mean % predicted (SD)[b]	57.1 (18.4)	57.38 (18.5)	51.03 (17.5)	55.18 (18.3)
Previous AF use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
AF naïve, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Supplemental oxygen therapy, n (%)	14 (16.1)	11 (12.5)	17 (19.5)	42 (16.0)

Key: AF, antifibrotic; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; nera, nerandomilast; SD, standard deviation.
Notes: [a] Percentages may not total 100 because of rounding. [b] Values corrected for haemoglobin level.
Source: FIBRONEER-IPF CTR (Tables 15.1.7.6: 2–15.1.7.6: 4);[20] Richeldi et al. 2025.[19]

Table 9 Baseline characteristics of patients, FIBRONEER-ILD ('no AF background therapy' cohort) [Reproduced from Table 6 of the CS]

Characteristic	Nera 18 mg bid N = 220	Nera 9 mg bid N = 220	Placebo N = 222	Total N = 662
Male sex, n (%)	111 (50.5)	103 (46.8)	116 (52.3)	330 (49.8)
Age, mean (SD), years	65.5 (10.2)	66.8 (10.2)	66.2 (10.8)	66.2 (10.4)
Weight, mean (SD), kg	70.4 (15.6)	70.3 (16.5)	70.5 (17.9)	70.4 (16.7)
Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Black/African American, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Multiple, n (%)	0 (0)	3 (1.4)	2 (0.9)	5 (0.8)
Smoking status, n (%)[a]				
Never smoked	114 (51.8)	127 (57.7)	123 (55.4)	364 (55.0)
Former smoker	98 (44.5)	88 (40.0)	94 (42.3)	280 (42.3)
Current smoker	8 (3.6)	5 (2.3)	5 (2.3)	18 (2.7)
Time since diagnosis of PPF, mean (SD), years	4.0 (4.2)	4.1 (4.4)	3.9 (3.6)	4.0 (4.1)
Underlying ILD diagnoses, n (%):				
Autoimmune ILDs	70 (31.8)	73 (33.2)	71 (32.0)	214 (32.3)
Hypersensitivity pneumonitis	30 (13.6)	42 (19.1)	39 (17.6)	111 (16.8)
Unclassifiable idiopathic interstitial pneumonia	40 (18.2)	44 (20.0)	36 (16.2)	120 (18.1)
Idiopathic non-specific interstitial pneumonia	55 (25.0)	42 (19.1)	40 (18.0)	137 (20.7)
Other ILDs	25 (11.4)	19 (8.6)	36 (16.2)	80 (12.1)
Baseline UIP or UIP-like fibrotic pattern	154 (70.0)	162 (73.6)	158 (71.2)	474 (71.6)
Other fibrotic pattern	66 (30.0)	58 (26.4)	64 (28.8)	188 (28.4)
FVC				
Mean value (SD), mL	2,354 (715)	2244 (759)	2264 (740)	2,287 (738)
Mean % predicted (SD)	72.4 (15.8)	70.9 (16.0)	70.1 (16.0)	71.1 (16.0)
DL_{CO}, mean % predicted (SD)[b]	52.8 (17.4)	52.3 (16.3)	52.4 (16.5)	52.5 (16.7)
Previous AF use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
AF naïve, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	Nera 18 mg bid N = 220	Nera 9 mg bid N = 220	Placebo N = 222	Total N = 662
Supplemental oxygen therapy, n (%)	45 (20.5)	38 (17.3)	44 (19.8)	127 (19.2)

Key: AF, antifibrotic; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IPD, important protocol deviations; nera, nerandomilast; PPF, progressive pulmonary fibrosis; SD; standard deviation; UIP, usual interstitial pneumonia.
Notes: [a] Percentages may not total 100 because of rounding. [b] Values corrected for haemoglobin level.
Source: FIBRONEER-ILD CTR (Tables 15.1.7.6: 2–15.1.7.6: 4);[21] Maher et al. 2025.[17]

3.2.2 Primary and secondary efficacy endpoints

The outcome measures listed in the NICE final scope for this appraisal were: pulmonary function; physical function, exacerbation rate, hospitalisations, mortality, adverse events of treatment, and health-related quality of life (HRQoL).

The main analysis was conducted following the first database lock (DBL1), with data cut-off dates of 16 August 2024 for FIBRONEER-IPF and 18 December 2024 for FIBRONEER-ILD, after the last randomised patient had completed the Week 52 assessment. The final analysis was conducted after the second database lock (DBL2), with cut-off dates of [redacted] for FIBRONEER-IPF and [redacted] for FIBRONEER-ILD, after the last patient had completed the trial.

Primary endpoints: Change from baseline in forced vital capacity (FVC) (mL)

The primary endpoint of FIBRONEER trials was the absolute change from baseline in FVC (mL) at Week 52. In the FIBRONEER-IPF trial, the adjusted mean change in FVC at Week 52 was -79.2 mL for the N group (n = 87) and -148.7 mL for the placebo group (n = 87), with a difference of 69.4 mL (95% CI -12.3-151.2). Similarly, in the FIBRONEER-ILD trial, the adjusted mean change in FVC at Week 52 was -95.2 mL for the N group (n = 220) and -154.1 mL for the placebo group (n = 222), with a difference of 58.9 mL (95% CI 12.1-105.8). The company considers both differences to represent a clinically meaningful reduction in lung function decline.

The adjusted annual rate of FVC decline up to 88 weeks was lower in the nerandomilast 18 mg bid group than in the placebo group ([redacted] vs. [redacted]), with a difference of [redacted] (95% CI [redacted]) in FIBRONEER-IPF. Similarly, in FIBRONEER-ILD, the adjusted annual rate of FVC decline over 52 weeks was lower in the nerandomilast 18 mg bid group than in the placebo group ([redacted] vs. [redacted]), with a difference of [redacted] (95% CI [redacted]).

Secondary endpoints: Time to the first occurrence of acute IPF/ILD exacerbation, first hospitalisation for respiratory cause or death over the duration of the trial

The key secondary endpoint was the time to the first occurrence of any of the following components of the composite endpoint: time to first acute (IPF or ILD) exacerbation, first hospitalisation for respiratory cause or death (whichever occurred first).

In the full analysis set (FAS), the key secondary endpoint was not met in either the FIBRONEER-IPF or FIBRONEER-ILD trials.

In the FIBRONEER-IPF trial, among participants not taking background AF therapy (monotherapy population in the CS), key secondary endpoint up to DBL2 occurred in 19/87 (21.8%) participants in the nerandomilast 18 mg bid group compared with 32/87 (36.8%) in the placebo group. Although the difference did not reach statistical significance, it was considered clinically meaningful by the company, favouring the 18 mg group (HR 0.62; 95% CI 0.35–1.10). Of the individual components of the key secondary endpoint, time to death was significantly improved in the nerandomilast 18 mg bid group compared with placebo (HR 0.26, 95% CI 0.07, 0.91).

Similarly, in the monotherapy population in FIBRONEER-ILD, key secondary endpoint events up to DBL2 were less likely to occur in the nerandomilast 18 mg bid group compared with placebo (55/220 (25%) vs. 83/222 (37.4%), HR 0.65, 95% CI 0.46, 0.92). Among the individual components of the key

secondary endpoint, the nerandomilast 18 mg bid group showed significant improvements compared with placebo, including reductions in the risk of first acute ILD exacerbation or death (HR 0.57, 95% CI 0.37-0.90), time to first hospitalisation for respiratory cause or death (HR 0.63, 95% CI 0.44-0.91), time to first hospitalisation for respiratory cause (HR [redacted]), and time to death (HR 0.44, 95% CI 0.24-0.81).

Secondary endpoints: Change from baseline in FVC % predicted and DLco % predicted

In both the FIBRONEER-IPF and FIBRONEER-ILD trials, the adjusted mean (standard error [SE]) change from baseline in FVC % predicted at Week 52 was numerically lower in the nerandomilast 18 mg bid group compared with placebo (FIBRONEER-IPF: [redacted], difference [redacted]; FIBRONEER-ILD: [redacted], difference [redacted]).

At Week 52, the adjusted mean (SE) change from baseline in DLco % predicted was numerically lower with nerandomilast 18 mg bid versus placebo in FIBRONEER-IPF, but slightly higher with nerandomilast 18 mg bid versus placebo in FIBRONEER-ILD (FIBRONEER-IPF: [redacted], difference [redacted]; FIBRONEER-ILD: [redacted], difference [redacted]).

At DBL2, composite endpoints in both FIBRONEER trials—time to absolute decline from baseline in FVC % predicted of >10% or death (FIBRONEER-IPF: HR 0.66, 95% CI 0.40-1.09; FIBRONEER-ILD: HR [redacted]) and time to absolute decline from baseline in DLco % predicted of >15% or death (FIBRONEER-IPF: HR 0.76, 95% CI 0.41-1.41; FIBRONEER-ILD: HR [redacted]) — were numerically lower in the nerandomilast 18 mg bid group than in the placebo group.

A summary of primary and secondary outcomes is presented in Table 10 below.

Table 10 Summary of the outcomes assessed in the FIBRONEER trials ('no AF background therapy' cohort) [Adapted from Tables 10-14, Figures 8, 10, 12, 14, Section 2 of the CS]

Outcome	Summary statistic	FIBRONEER-IPF			FIBRONEER-ILD		
		Placebo n=87	Nerandomilast 18 mg bid n=87	Nerandomilast 9 mg bid n=86	Placebo n=222	Nerandomilast 18 mg bid n=220	Nerandomilast 9 mg bid n=217
Primary endpoint							
Change from baseline in FVC (mL) at Week 52	Adjusted mean change from baseline (mL)	-148.7	-79.2	-70.4	-154.1	-95.2	-82.3
	Difference vs. placebo (95% CI)	--	69.4 (-12.3, 151.2)	78.3 (-3.2, 159.8)	--	58.9 (12.1, 105.8)	71.8 (24.9, 118.8)
Key secondary endpoint							
Time to first occurrence of acute exacerbation, first hospitalisation for respiratory cause or death up to DBL2	N with events/ N analysed	32/87	19/87	--	83/222	55/220	--
	HR (95% CI)	--	0.62 (0.35, 1.10)	--	--	0.65 (0.46, 0.92)	
Other secondary endpoints							
Time to first acute exacerbation or death up to DBL2	N with events/ N analysed	21/87	12/87	--	55/222	30/220	--
	HR (95% CI)	--	0.66 (0.32, 1.35)	--	--	0.57 (0.37, 0.90)	--
Time to first hospitalisation for a respiratory cause or death up to DBL2	N with events/ N analysed	28/87	16/87	--	76/222	49/220	--
	HR (95% CI)	--	0.57 (0.31, 1.06)	--	--	0.63 (0.44, 0.91)	--

Outcome	Summary statistic	FIBRONEER-IPF			FIBRONEER-ILD		
		Placebo n=87	**Nerandomilast 18 mg bid n=87**	**Nerandomilast 9 mg bid n=86**	**Placebo n=222**	**Nerandomilast 18 mg bid n=220**	**Nerandomilast 9 mg bid n=217**
Time to death up to DBL2	N with events/ N analysed	12/87	3/87	--	36/222	15/220	--
	HR (95% CI)	--	0.26 (0.07, 0.91)	--	--	0.44 (0.24, 0.81)	--
Change from baseline in FVC % predicted at Week 52	N analysed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean change (mL)						
	Difference vs. placebo (95% CI)	–	[redacted]	[redacted]	–	[redacted]	[redacted]
Change from baseline in DLco % predicted at Week 52	N analysed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted mean change (mL)						
	Difference vs. placebo (95% CI)	–	[redacted]	[redacted]	–	[redacted]	[redacted]
Time to absolute decline in FVC % predicted of >10% or death up to DBL2	N with events, n (%)	37 (42.5)	26 (29.9%)	25 (28.4)	[redacted]	[redacted]	[redacted]
	HR (95% CI)	--	0.66 (0.40, 1.09)	0.65(0.39, 1.08)	--	[redacted]	[redacted]
Time to absolute decline in DLco % predicted of >15% or death up to DBL2	N with events, n (%)	21 (24.1)	20 (23.0)	17 (19.3)	[redacted]	[redacted]	[redacted]
	HR (95% CI)	--	0.76 (0.41, 1.41)	0.61 (0.32, 1.17)	--	[redacted]	[redacted]

Key: bid, twice a day; CI, confidence interval; DBL2, second database lock; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HR, hazard ratio; N, number; SE, standard error.

HRQoL

Participants' health-related quality of life (HRQoL) was assessed using the Living with Pulmonary Fibrosis (L-PF) questionnaire (summary scores ranging from 0 to 100, with higher scores indicating greater impairment) and the EQ-5D.

In FIBRONEER-IPF, the adjusted mean change from baseline in the L-PF impact total score and symptom total score was approximately 1 point lower (indicating a slight improvement) in the treatment group than in the control group; however, the differences were small (impact: [redacted] vs [redacted], difference [redacted]; symptom: [redacted] vs [redacted], difference [redacted]).

Similar results were observed in FIBRONEER-ILD (impact: [redacted] vs [redacted], difference [redacted]; symptom: [redacted] vs [redacted], difference [redacted]), with even smaller differences, indicating that the groups were very similar.

With respect to the EQ-5D, the CS reports that there was no meaningful difference between the groups.

3.2.3 Subgroup analyses

The subgroup analyses listed in the NICE final scope for this appraisal were:

- IPF
- PPF
- Disease severity defined by FVC

Data for IPF and PPF are presented separately in Section 2.6 of the CS, consistent with the separate analyses conducted for the FIBRONEER-IPF and FIBRONEER-ILD studies.

Subgroup analyses based on baseline FVC % predicted (≤70% vs >70%) are conducted in the FAS population of FIBRONEER-IPF and FIBRONEER-ILD, including monotherapy and non-monotherapy groups, and presented in

Appendix C. The analyses indicate that treatment effect of nerandomilast 18 mg bid as compared with placebo are broadly consistent across subgroups.

3.2.4 Adverse events

The company reports adverse event (AE) data for nerandomilast from the FIBRONEER-IPF and FIBRONEER-ILD trials up to DBL1 and DBL2 in Section 2.11 and Appendix D of the CS. Equivalent summaries for the Treated Set (TS) population are provided in Appendix K and Appendix L, respectively. Key adverse event outcomes are summarised in Table 11.

Nearly all participants in both the FIBRONEER-IPF and FIBRONEER-ILD trials experienced treatment-emergent adverse events (TEAEs). At the time of the second database lock (DBL2), the nerandomilast 18 mg bid group, compared with placebo, was associated with a lower proportion of serious AEs (FIBRONEER-IPF: [redacted]; FIBRONEER-ILD: [redacted]), serious AE resulting in death (FIBRONEER-IPF: [redacted]; FIBRONEER-ILD: [redacted]), AEs leading to treatment discontinuation (FIBRONEER-IPF: 9.2% vs 12.6%; FIBRONEER-ILD: 10.0% vs 12.2%), AEs leading to treatment interruption (FIBRONEER-IPF: [redacted]; FIBRONEER-ILD: [redacted]), and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥3) (FIBRONEER-IPF: [redacted]; FIBRONEER-ILD: [redacted]).

However, treatment-related adverse events (TRAEs) were more frequent in the nerandomilast 18 mg bid group than in the placebo group (FIBRONEER-IPF: [redacted]; FIBRONEER-ILD: [redacted]), as reported in the CS, primarily due to diarrhoea.

At DBL2, diarrhoea was the most frequently reported adverse event (AE) at the preferred term level across both trials, with a higher incidence in the nerandomilast 18 mg bid group than in the placebo group (FIBRONEER-IPF: 27.6% vs 8.1%; FIBRONEER-ILD: 27.3% vs 17.1%) (Tables 17 and 18, Appendix D). Other commonly reported AEs up to DBL2 in the 18 mg bid

group, compared with placebo, included COVID-19 ([redacted]) and upper respiratory tract infection ([redacted]) in FIBRONEER-IPF, and cough ([redacted]) and upper respiratory tract infection ([redacted]) in FIBRONEER-ILD.

The CS reported diarrhoea, weight decrease, drug-induced liver injury and psychiatric events as the most important AE of special interest (AESI).

- Although diarrhoea was reported more frequently in the nerandomilast 18 mg bid group than in the placebo group (as noted above), most cases were reported to be mild (CTCAE Grade 1). [redacted] Grade ≥3 events were observed in the FIBRONEER-IPF trial, and [redacted] Grade 3 events occurred in the FIBRONEER-ILD trial up to DBL2, [redacted] in the nerandomilast 9 mg group.

- Weight decrease was more frequently reported in the nerandomilast 18 mg bid group than in the placebo group at DBL1 (FIBRONEER-IPF: 8.0% vs. 5.7%; FIBRONEER-ILD: 12.7% vs. 5.0%) and DBL2 (FIBRONEER-IPF: [redacted] FIBRONEER-ILD: [redacted]) (Tables 17 and 18, Appendix D); none of the events were classified as serious AEs, severe AEs (CTCAE Grade 3), or AEs leading to treatment discontinuation (Table 23 of the CS).

- [redacted] in FIBRONEER-IPF and [redacted] in FIBRONEER-ILD were reported to have an AESI of 'potential severe DILI' up to DBL2; [redacted] of these cases occurred in the nerandomilast 18 mg bid group.

- The proportion of psychiatric disorder events at the System Organ Class (SOC) level was higher with 18 mg BID than with placebo at DBL2 in both trials (FIBRONEER-IPF: [redacted]; FIBRONEER-ILD: [redacted]; Table 24 of the CS), although this appears inconsistent with the CS statement that, in the FIBRONEER-ILD trial, the proportion was slightly lower with 18 mg bid than with placebo. The most common psychiatric events were depression and anxiety. Suicidal ideation was reported in [redacted] in FIBRONEER-IPF ([redacted]

receiving nerandomilast 18 mg bid and [redacted] receiving nerandomilast 9 mg bid) and in [redacted] in FIBRONEER-ILD ([redacted] receiving nerandomilast 18 mg bid and [redacted] receiving nerandomilast 9 mg bid). [redacted].

No completed suicide was observed in either trial.

Overall, the EAG clinical expert is of the opinion that the safety profile is consistent with that expected from the use of nerandomilast in this population and has no concerns.

Table 11 Overall summary of adverse events up to DBL1 and DBL2 in FIBRONEER trials ('no AF background therapy' cohort) [Adapted from Tables 20-23, Section 2.11, and Tables 17-18, Appendix D, of the CS]

	DBL1			DBL2		
	Nerandomilast 18 mg bid n (%)	Nerandomilast 9 mg bid n (%)	Placebo n (%)	Nerandomilast 18 mg bid n (%)	Nerandomilast 9 mg bid n (%)	Placebo n (%)
FIBRONEER-IPF						
N analysed	87	88	87	87	88	87
Any AE	79 (90.8)	79 (89.8)	85 (97.7)	[redacted]	[redacted]	[redacted]
Most frequent event[†]						
COVID-19	--	--	--	[redacted]	[redacted]	[redacted]
URT infection	--	--	--	[redacted]	[redacted]	[redacted]
Nasopharyngitis	--	--	--	[redacted]	[redacted]	[redacted]
Pneumonia	--	--	--	[redacted]	[redacted]	[redacted]
Bronchitis	--	--	--	[redacted]	[redacted]	[redacted]
Diarrhoea	23 (26.4)	15 (17.0)	7 (1.1)	24 (27.6)	15 (17.1)	7 (8.1)
Cough	--	--	--	[redacted]	[redacted]	[redacted]
Dyspnoea	--	--	--	[redacted]	[redacted]	[redacted]
Condition aggravated	--	--	--	[redacted]	[redacted]	[redacted]
Depression	--	--	--	[redacted]	[redacted]	[redacted]
Anxiety	--	--	--	[redacted]	[redacted]	[redacted]
AE leading to permanent treatment discontinuation						
Any	6 (6.9)	7 (8.0)	7 (8.1)	8 (9.2)	9 (10.2)	11 (12.6)

	DBL1			DBL2		
	Nerandomilast 18 mg bid n (%)	**Nerandomilast 9 mg bid n (%)**	**Placebo n (%)**	**Nerandomilast 18 mg bid n (%)**	**Nerandomilast 9 mg bid n (%)**	**Placebo n (%)**
Diarrhoea	[redacted]	[redacted]	[redacted]	1 (1.1)	0 (0)	0 (0)
AE leading to temporary treatment interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs‡						
Any	23 (26.4)	27 (30.7)	31 (35.6)	[redacted]	[redacted]	[redacted]
Resulted in death	0	3 (3.4)	8 (9.2)	[redacted]	[redacted]	[redacted]
FIBRONEER-ILD						
N analysed	220	220	222	220	220	222
Any AE	203 (92.3)	206 (93.6)	207 (93.2)	[redacted]	[redacted]	[redacted]
Most frequent event†						
URT infection	--	--	--	[redacted]	[redacted]	[redacted]
COVID-19	--	--	--	[redacted]	[redacted]	[redacted]
Pneumonia	--	--	--	[redacted]	[redacted]	[redacted]
Nasopharyngitis	--	--	--	[redacted]	[redacted]	[redacted]
Diarrhoea	59 (26.8)	35 (15.9)	35 (15.8)	60 (27.3)	39 (17.7)	38 (17.1)
Cough	--	--	--	[redacted]	[redacted]	[redacted]
Condition aggravated	--	--	--	[redacted]	[redacted]	[redacted]
Weight decreased	28 (12.7)	18 (8.2)	11 (5.0)	[redacted]	[redacted]	[redacted]
Depression	--	--	--	[redacted]	[redacted]	[redacted]
Anxiety	--	--	--	[redacted]	[redacted]	[redacted]

	DBL1			DBL2		
	Nerandomilast 18 mg bid n (%)	**Nerandomilast 9 mg bid n (%)**	**Placebo n (%)**	**Nerandomilast 18 mg bid n (%)**	**Nerandomilast 9 mg bid n (%)**	**Placebo n (%)**
AE leading to permanent treatment discontinuation						
Any	21 (9.6)	22 (10.0)	28 (12.6)	22 (10.0)	25 (11.4)	27 (12.2)
Diarrhoea	[redacted]	[redacted]	[redacted]	3 (1.4)	0 (0)	0 (0)
AE leading to temporary treatment interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs‡						
Any	80 (36.4)	85 (38.6)	98 (44.1)	[redacted]	[redacted]	[redacted]
Resulted in death	5 (2.3)	14 (6.4)	16 (7.2)	[redacted]	[redacted]	[redacted]

Key: AE, adverse events; N, number; URT, upper respiratory tract

† Adverse events that were reported in more than 10% of the patients in any of the trial groups

‡ Serious adverse events refer to events that have major clinical consequences, such as resulting in death, being life-threatening, requiring inpatient hospitalisation or prolongation of hospitalisation, resulting in persistent or significant disability or incapacity, and/or requiring medical or surgical intervention to prevent death, disability or hospitalisation.[22]

3.2.5 Meta-analyses

Section 2.9 of the CS presented results for pooled independent patient-level data (IPD) analyses of FIBRONEER-IPF and FIBRONEER-ILD in the monotherapy population. The main results from this pooled analysis were as follows:

- Adjusted mean difference in change from baseline to Week 52 in FVC of [redacted] (95% CI: [redacted]) representing a [redacted] relative reduction in lung function decline.
- Hazard ratio of time to the first occurrence of acute exacerbation, first hospitalisation for respiratory cause or death versus placebo of [redacted]).
- Hazard ratio of first acute exacerbation or death versus placebo of [redacted]).
- Hazard ratio of hospitalisation for respiratory cause or death versus placebo [redacted]).
- Hazard ratio of death versus placebo of [redacted]).
- Hazard ratio of time to FVC % predicted decline of > 10% or death versus placebo of [redacted]).

These results are illustrated graphically in Figures 22 to 25 of the CS.

3.3 Critique of the results of the trials of the technology of interest

3.3.1 Critique of statistical methods employed in the trials of interest

The primary endpoint in the two main trials presented in the CS (absolute change from baseline in FVC (mL) at Week 52) was analysed using a mixed-effects model for repeated measures with a restricted maximum likelihood approach. In response to clarification, the company stated that patient visit was treated as the repeated measure and that an unstructured covariance structure was used to model the within-patient measurements.

For the key secondary outcome, the company used a Cox proportional hazard model to estimate hazard ratios of a composite endpoint, defined as the first occurrence of acute exacerbation, respiratory-related hospitalisation, or death. The EAG questioned why a competing risk approach was not used for these outcomes. In its clarification response, the company stated that the Cox proportional hazards model had been prespecified in the FIBRONEER trials for time-to-event endpoints. The company also argued that because death was included as a component of the composite endpoint, competing risk methods were not required. Moreover, they argued that while death precludes the occurrence of the other components, acute exacerbation and hospitalisation did not preclude subsequent events. The company further stated that the Fine–Gray competing risks model has statistical and interpretability limitations.

The EAG remains concerned that in a Cox model, censoring patients at death treats death as non-informative right-censoring. This assumes that the risk of the non-fatal event for those who died is the same as for those who remain under observation. This may create an unquantifiable bias in the estimate of the non-fatal event risk. In the view of the EAG, this potential bias may outweigh the statistical or interpretability concerns associated with a competing risk approach.

The CS stated that multiplicity-adjusted analyses were used for the primary and key secondary endpoints. In response to clarification, the company explains that alpha control was adjusted through hierarchical testing of primary and key secondary endpoint for both 18 mg and 9 mg doses, rather than through simultaneous testing.

In the first step of testing (for the primary endpoint), alpha was split between the two primary endpoint comparisons: 0.04 was assigned to the 18 mg primary endpoint test, and 0.01 was assigned to the 9 mg primary endpoint test. Once the primary endpoint for the 18 mg dose was statistically significant, the alpha was further reallocated between the 9 mg primary endpoint and the 18 mg key secondary endpoint (as detailed graphically in Figure 1 of the company's response to clarification).

While the EAG agrees that this approach is consistent with the closed testing principle, as stated by the company, no clear rationale was provided for assigning 4% alpha to the primary endpoint in a 1:1:1 trial.

3.3.2 Critique of the main results of the trials

Baseline demographic and clinical characteristics of participants of both FIBRONEER trials were broadly similar, and the EAG has no major concerns about adequate randomisation in these trials.

Results of the primary and secondary endpoints are described and tabulated in a previous section (3.2.2).

The primary endpoint of change in FVC (ml) from baseline at week 52 shows a significant advantage of nerandomilast over placebo in both IPF and ILD patients. *The EAG notes that the computed confidence intervals are quite wide, reflecting uncertainty in the observed estimates*.

The key secondary endpoint of time to the first occurrence of acute exacerbation, first hospitalisation for respiratory cause or death did not show statistically significant advantage for patients on nerandomilast monotherapy over placebo in the FIBRONEER-IPF trial, although the company considered the point estimate to be clinically meaningful. *The EAG notes the relatively wide confidence interval around this estimate, reflecting the uncertainty around this estimate*. For the FIBRONEER-ILD monotherapy population, the key secondary endpoint was significant for nerandomilast compared with placebo.

Other secondary endpoints broadly favoured nerandomilast, but the majority failed to reach statistical significance with wide confidence intervals in the FIBRONEER-IPF

trial. Only time to death up to DBL2 (nerandomilast 18mg) and change from baseline in FVC % predicted at Week 52 (nerandomilast 9mg) achieved significance in the FIBRONEER-IPF trial.

In the FIBRONEER-ILD trial, all other secondary outcomes reached significance for nerandomilast 18mg except change from baseline in DLco % predicted at Week 52 and time to absolute decline in DLco % predicted of >15% or death up to DBL2. For the 9mg dose, for the secondary endpoints assessed, change from baseline in FVC % predicted at Week 52 and time to absolute decline in FVC % predicted of >10% or death up to DBL2 reached significance.

The company states in its submission that no multiplicity-adjusted analyses were performed on these secondary outcomes and as such the results should be considered exploratory. *The EAG is broadly in agreement with this line of assessment*.

The pooled IPD analysis of the FIBRONEER trials in the monotherapy population provides evidence that nerandomilast significantly slows disease progression as measured by reduced FVC decline, compared with placebo. It also suggests that nerandomilast reduces the risk of time to the first occurrence of acute exacerbation, first respiratory-related hospitalisation or death. Moreover, nerandomilast was associated with significantly reductions in the risk of first acute exacerbation or death, respiratory-related hospitalisation or death, death alone, and time to FVC % predicted decline of > 10% or death, compared with placebo.

In the view of the EAG, these results provide evidence of the benefits of nerandomilast over placebo, though uncertainties remain around the estimates and statistical approaches to analysis.

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

The company considered IPD meta-regression, Bucher pairwise comparisons, and Bayesian network meta-analysis (NMA) in its approach to conducting indirect treatment comparisons. The company states that due to the availability of IPD, a meta-regression was considered most robust for both IPF and PPF and focuses on

this in the submission and in the economic model (Section 2.10.3 of the company evidence submission document and the technical report of IPD meta-regression for nerandomilast versus nintedanib in patients with IPF and PPF).

The EAG agrees that, where IPD is available, it provides for the most robust methodology in indirect comparisons and should be preferred over other aggregate data-dependent methods.

3.4.1 Included studies in the IPD meta-regression

The INPULSIS 1 and 2 [IPF] and INBUILD [PPF]) were Phase III RCTs that evaluated the efficacy of nintedanib 150mg twice daily against placebo.

INPULSIS-1 (NCT01335464) and INPULSIS-2 (NCT01335477) were two parallel, Phase 3, randomised, double-blind, placebo-controlled trials that evaluated the efficacy and safety of nintedanib in patients with IPF. The studies were conducted across 205 sites in 24 countries, spanning 5 continents. The baseline clinical and demographic characteristics were similar to the FIBRONEER-IPF trial previously described, with participants in the INPULSIS trials slightly younger than in the FIBRONEER-IPF trial ([redacted] vs. [redacted] for the NDB and nerandomilast 18mg arms, respectively) and a higher proportion of participants in Europe ([redacted] vs. [redacted] for the 150mg nintedanib and nerandomilast 18mg arms, respectively).

The INBUILD trial (NCT02999178) was a randomised, double-blind, placebo-controlled, parallel-group Phase 3 study designed to evaluate the efficacy and safety of nintedanib in patients with ILDs other than IPF. The study was conducted at 153 sites across 15 countries. The baseline characteristics for the FIBRONEER-ILD and INBUILD trials were broadly similar apart from the proportion of participants in Europe, which was higher in the 150mg nintedanib arm of the INBUILD study than the 18mg nerandomilast arm of the FIBRONEER study ([redacted] vs. [redacted] respectively).

3.4.2 Studies included in the Bayesian NMA and Buchar pairwise comparisons.

The company also provides results for the Bucher pairwise comparisons and Bayesian NMA in the aggregate data-based ITC technical report in the reference

pack. Aggregated data were from five additional trials investigating pirfenidone or nintedanib therapy for the treatment of IPF

- ASCEND: Pirfenidone vs Placebo
- CAPACITY 1: Pirfenidone vs Placebo
- CAPACITY 2: Pirfenidone vs Placebo
- JAPICCTI-050121: Pirfenidone vs Placebo
- TOMORROW: Nintedanib vs Placebo

While population inclusion criteria were broadly consistent across all studies, there was some heterogeneity in study design and outcome assessment. These include:

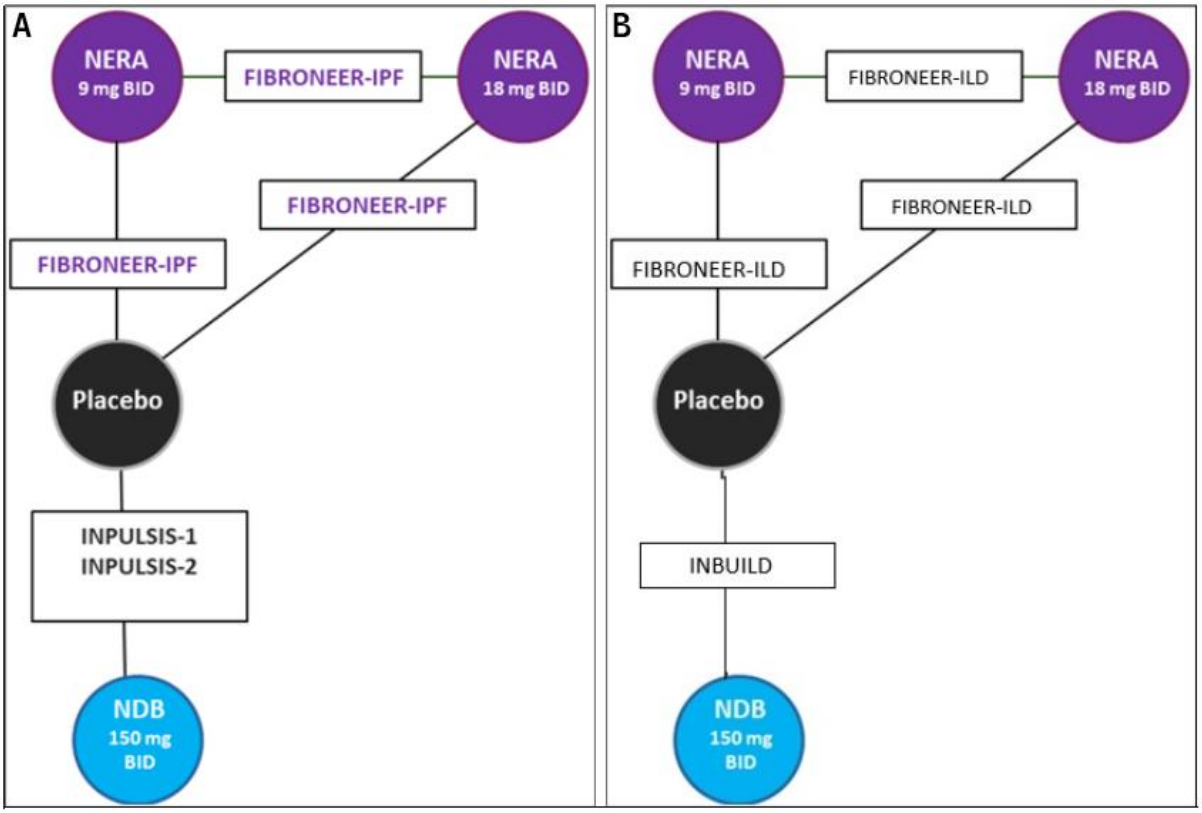
- Study design: All were Phase 3 double-blind randomised controlled trials, except TOMORROW, which was a Phase 2 trial. All studies were global multicentre studies, except JAPICCTI-050121, which was a multicentre study conducted in Japan. The enrolment periods span over 20 years across studies, ranging from 2004–2005 (JAPICCTI-050121) to 2022–2025 (FIBRONEER-IPF).
- Outcome assessment: Most studies reported outcomes of interest at 52 weeks, whereas CAPACITY 1 and CAPACITY 2 reported decline ≥10 percentage points in FVC % predicted, serious AE and discontinuation at 72 weeks, and % predicted FVC at 60 and 72 weeks.
- Patient characteristics: Age and sex were comparable across studies. Some differences were observed in FVC % predicted and DLco % predicted between FIBRONEER-IPF and the comparator trials, with higher values reported in FIBRONEER-IPF.

All studies except JAPICCTI-050121 were judged to be at low risk of bias across all domains, with JAPICCTI-050121 being at unclear risk of bias for randomisation and concealment of allocation domains.

3.5 Critique of the indirect comparison or multiple treatment comparison

3.5.1 IPD meta-regression

The network diagram for the IPD meta-regression for IPF and PPF is shown in Figure 6.



Key: BID, twice a day; DBL2, database lock 2; ILD, interstitial lung disease; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib; NERA, nerandomilast; PPF, progressive pulmonary fibrosis.
Notes: IPD meta-regression used DBL2 data from all trials.
Source: Technical report for IPD meta-regression.

Figure 6 Network diagrams for IPD meta-regression for (A) IPF and (B) PPF [Reproduced from Figure 26 of the CS]

Variable selection was based on identification of potential effect modifiers and confounders in published subgroup analyses and NMA, HTA submissions,

previously conducted feasibility assessments and feedback from clinical experts. Variable inclusion can be seen in Table 18 of the company's submission.

The IPD meta-regression was implemented in a one-step approach that used linear mixed-effects models for continuous outcomes (change from baseline in FVC mL, and percent predicted at 52 weeks), Cox proportional hazards for time -to-event outcomes (death, first acute exacerbation, first ≥10% FVC % predicted decline, respiratory-related death), logistic regression for several secondary binary outcomes. Table 2, Section 3.2.3 of the IPD meta-regression technical report provides a comprehensive list of the outcomes used and the analysis approach.

Variables were centred to the overall mean values from the combined FIBRONEER and INPUSIS/INBUILD trials. Study (FIBRONEER versus INPULSIS/INBUILD) was included in the model as a fixed effect, with FIBRONEER-IPF and FIBRONEER-ILD set as the reference categories for IPF and PPF, respectively.

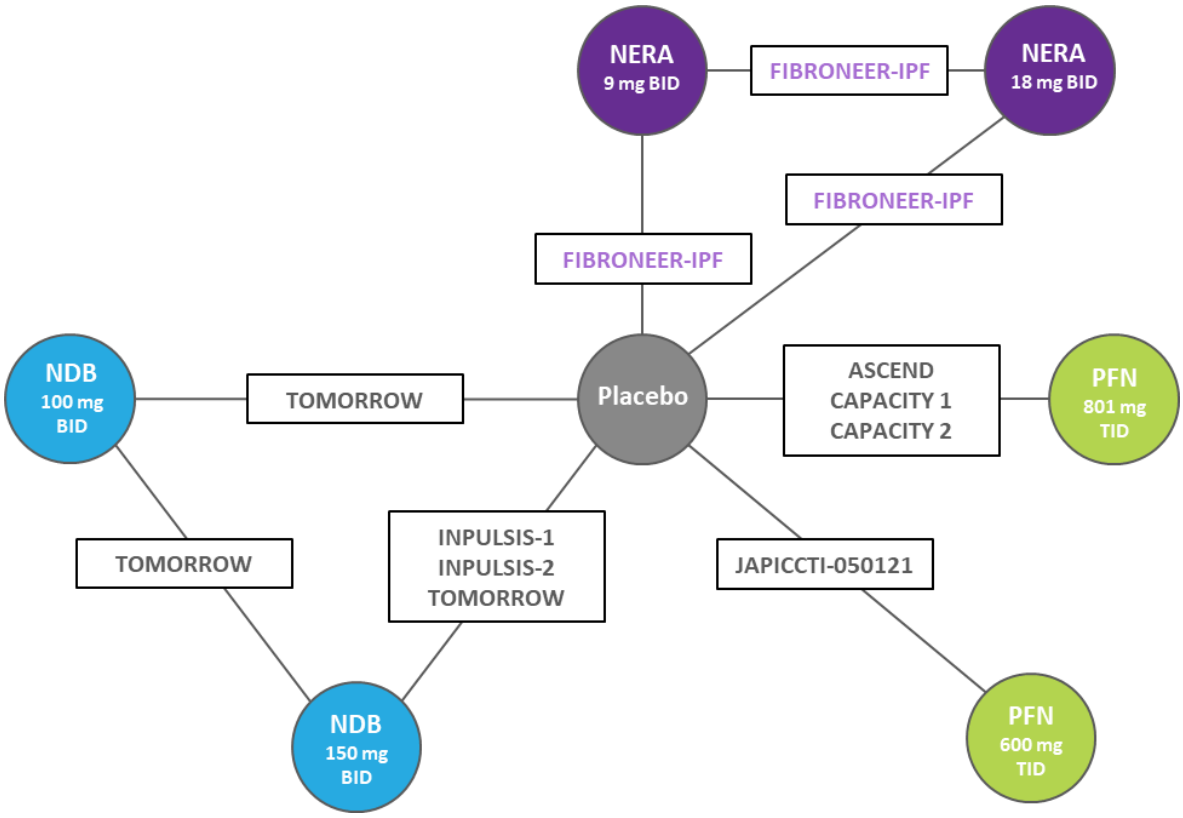
The company focuses on the IPD meta-regression for ITC of nerandomilast and nintedanib, as this was the data available.

3.5.2 Bayesian NMA and Bucher pairwise comparisons.

Aggregate data ITCs were done where IPD was not available (for pirfenidone) using the Bucher pairwise comparisons and Bayesian NMA. A network diagram is presented in Figure 7.

Fixed and random effects Bayesian NMAs were conducted for all outcomes of interest with the assumption that the true effects are randomly distributed around some population mean effect. Bayesian analyses were carried out performing Markov Chain Monte-Carlo (MCMC) simulations.

Bucher ITC was conducted in two stages. First, results from multiple trials for each pair-wise comparison were pooled to obtain the direct estimate for the comparison and its standard error using classical (frequentist) meta-analysis. The random-effects model was used as the primary analysis to account for any unexplained heterogeneity in the trial’s population and study estimates. In the second stage, the direct estimates of two treatments versus the common comparator, placebo, was used to compute the indirect estimate of one treatment vs another.



Key: BID, twice a day; NDB, nintedanib; NERA, nerandomilast; PFN, pirfenidone.
Source: ITC feasibility assessment report.[23]

Figure 7 Network diagram for Bayesian NMA (IPF)

3.5.3 Results of indirect treatment comparisons

Table 12 presents the relative effects of nerandomilast 18 mg bid versus nintedanib 150 mg bid in IPF and PPF derived from IPD meta-regression for the main clinical efficacy outcomes. The results show no statistically significant differences between the efficacy of nerandomilast and NDB. The company highlight clinically meaningfully lower risk of mortality compared with nintedanib 150 mg bid in both IPF (HR: [redacted]) and PPF (HR: [redacted]).

However, as these results do not reach statistical significance, there is considerable uncertainty around these estimates.

Table 12 Overview of key results from IPD meta-regression for nerandomilast 18 mg bid versus nintedanib 150 mg bid [Reproduced from Table 19 of the CS]

Nerandomilast 18 mg bid vs nintedanib 150 mg	IPF	PPF
Time to event over the whole trial duration, hazard ratio (95% CI)		
Time to death	[redacted]	[redacted]
Time to first acute exacerbation	[redacted]	[redacted]
Time to first ≥10% FVC % predicted decline	[redacted]	[redacted]
Time to respiratory related death	[redacted]	[redacted]
Absolute change from baseline at 52 weeks, mean difference (95% CI)		
FVC (mL)	[redacted]	[redacted]
FVC % predicted	[redacted]	[redacted]
Rate over the whole trial duration, relative rate (95% CI)		
Rate of progression	[redacted]	[redacted]

Key: bid, twice a day; CI, confidence interval; FVC, forced vital capacity; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.
Notes: *Indicates numerical benefit in favour of nerandomilast.
Source: Technical Report for IPD meta-regression.[24]

Table 13 presents an overview of the results of the Bucher ITC and Bayesian NMA for the main clinical efficacy outcomes. The results demonstrate no statistical significance of the effectiveness of nerandomilast over nintedanib of pirfenidone.

As none of these results reaches statistical significance, this indicates substantial uncertainty about the effectiveness of nerandomilast over the comparators. Wide confidence intervals for many of the results increase this level of uncertainty further, and it is not possible without further data to make a determination of the effectiveness (or otherwise) of nerandomilast over its comparators.

Table 13 Results of indirect treatment comparisons random effects for main outcomes of IPF patients for nerandomilast 18 mg bid versus nintedanib 150 mg bid and vs pirfenidone 801 mg [Collated from Indirect Treatment Comparison - Network Meta-Analysis Report; Section 3.2, 3.3, page 26-43)

	Bucher Indirect Treatment Comparisons		Bayesian Network Meta-Analysis	
	vs nintedanib 150 mg	**vs pirfenidone 801 mg**	**vs nintedanib 150 mg**	**vs pirfenidone 801 mg**
Time to event, HR (95% CrI)				
Time to death over the whole trial duration	[redacted]	[redacted]	[redacted]	[redacted]
Time to first acute exacerbation over the whole trial duration	[redacted]	-	[redacted]	-
Odds of event, OR (95% CrI)				
Decline ≥10% in FVC % predicted	[redacted]	[redacted]	[redacted]	[redacted]
Deaths at 52 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory related deaths at 52 weeks	[redacted]	-	[redacted]	-
Absolute change from baseline at 52 weeks, MD (95% CrI)				
FVC (mL)	[redacted]	[redacted]	[redacted]	[redacted]
FVC % predicted	[redacted]	[redacted]	[redacted]	[redacted]

Key: bid, twice a day; HR, hazard ratio; OR, odds ratio; MD, mean difference; CrI, credible interval; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.

It is the view of the EAG that the company's approach to analysis of the ITC is comprehensive and robust. The EAG is satisfied that, for the trials where IPD is available, meta-regression is the most robust approach for the treatment comparison.

While the EAG acknowledges that IPD provides the most robust approach for the ITC, the exclusion of pirfenidone from the meta-regression, where only aggregate data were available, meant that the company assumed equivalence between pirfenidone and nintedanib. This is an area of significant concern. Although the NMA estimates were broadly directionally consistent with the IPD meta-regression estimates, where these were available, they differed to an extent that could affect the economic model. The EAG considers that assuming equivalence between pirfenidone and nintedanib carries a greater risk of bias than the assumptions required to conduct aggregate data-based ITCs. Therefore, estimates from the Bayesian NMA should be reported and used for pirfenidone where IPD is not available.

3.6 Additional work on clinical effectiveness done by the EAG

No additional work has been done by the EAG for the clinical effectiveness section.

3.7 Conclusions of the clinical-effectiveness section

The company submission represents a comprehensive review of the evidence of the clinical effectiveness of nerandomilast. The company has considered all relevant available evidence and assessed outcomes broadly in line with the NICE scope.

The company submission provides evidence of the superiority of nerandomilast over best supportive care with a significant advantage in the primary outcome of change from baseline in FVC (ml) at week 52. The key secondary outcome of the FIBONEER trials of the composite endpoints comprising time to the first acute exacerbation, first respiratory-related hospitalisation or death showed an advantage for nerandomilast, though this was not significant in IPF patients. Exploratory secondary analysis showed mixed results, with many effects failing to reach statistical significance.

There is concern about the use of a Cox regression approach, rather than a competing risk approach, for some non-fatal outcomes.

The company focused on the results of the IPD-NMR that compared nerandomilast with nintedanib but did not have access to IPD for pirfenidone and consequently assumed equivalence between the two main comparators. They have also appended results from ITC using aggregated data in the technical report of the ITC-NMA. Results of the NMR are broadly in the same direction as those obtained from the NMA, though the estimates and CIs differed substantially in some cases. This, along with the lack of precision in the reported confidence and credible intervals, constitutes substantial uncertainty around the results.

None of the treatment effects for nerandomilast versus its comparators, reported for the main outcomes in the ITC analyses, reached statistical significance. Therefore, substantial uncertainty remains regarding the effectiveness of nerandomilast compared with either nintedanib or pirfenidone.

4 Cost effectiveness

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of the cost-effectiveness evidence and section 4.2 covers the company's economic evaluation.

4.1 Critique of the review of cost-effectiveness evidence

Appendix E of the company submission details the methods and results of systematic literature searches, conducted in September 2025, to identify cost, resource use, QoL, utility and economic evaluation studies of IPF and PPF treatments. Searches were conducted in line with the PICOS criteria, and the review was registered with PROSPERO.[25] Detailed search strategies for cost, resource use and economic evaluation studies are provided in Appendix E.1.1. Search strategies for QoL and utilities studies are provided in Appendix E.1.2. PRISMA charts for the reviews are available in Figures 14 (cost, resource use and economic evaluations) and 15 (QoL and utilities) respectively.

The company's searches identified N=9 economic evaluations for IPF and N=2 for PPF. Full details of the studies are provided in Appendix E.5. Briefly, for IPF, three studies were conducted in the UK, of which all were cost-utility analyses. Two studies were decision analytical models over a lifetime horizon, and potentially relevant for the current assessment, adopting a healthcare system perspective.[26, 27] Rinciog et al. compared Pirfenidone and Nintedanib vs. BSC, and Pirfenidone vs. Nintedanib. At list prices for all comparators, the ICERs were Pirfenidone vs. BSC (£172, 198); Nintedanib vs. BSC (£145, 310).[26] Pirfenidone was found to be dominated by Nintedanib. Loveman et al. found similar conclusions, with ICERs for Pirfenidone vs. BSC (£190, 146); Nintedanib vs. BSC (£132, 658).[27]

For PPF, none of the identified economic evaluations were conducted in the UK, but the EAG notes a CADTH assessment.

The EAG is satisfied that the company's search strategy is appropriate to identify all the relevant economic evidence for IPF and PPF. The EAG notes that there are no published economic evaluations of nerandomilast and so it is appropriate to develop

a de novo model for this assessment. The EAG's critique of the relevant evidence on healthcare resource use, costs and utilities is provided in Sections 4.2.6 and 4.2.7.

The company has identified 4 relevant NICE technology appraisals to this decision problem:

- TA504 (Pirfenidone vs. Nintedanib or BSC, for IPF),
- TA379 (Nintedanib vs. Pirfenidone or BSC, for IPF – FVC 50-80% predicted),
- TA864 (Nintedanib vs. established clinical management, for IPF - FVC >80% predicted)
- TA747 (Nintedanib vs. established clinical management, for PPF that has progressed despite treatment)

The EAG is satisfied that these are the most relevant NICE appraisals for which to compare the current assessment. EAG comparison of the current assessment against previous NICE appraisals is embedded throughout each section of the report where relevant.

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

The EAG's assessment of the company submission against the NICE reference case is summarised in Table 14 below.

Table 14 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	Perspective of carers not included
Perspective on costs	NHS and Personal Social Services	yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	yes
Synthesis of evidence on health effects	Based on systematic review	yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	yes
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	yes

4.2.2 Model structure

The model is an Excel-based Markov-cohort model, with ten modelled Markov health states defined by 10-point FVC % predicted ranges. Health states range from best FVC % predicted state (>110% FVC % predicted) to the worst state (30–39.9% FVC % predicted). The cohort enter the model with a distribution across FVC % predicted states according to the baseline data from the respective FIBRONEER trials. In each 3-monthly cycle, the cohort can experience progression (reduction of FVC % predicted) over time, until they enter the worst FVC % predicted state, where they remain or enter the death state. Despite some suggestion of improvements in FVC % predicted from the FIBRONEER trial data for nerandomilast, regression of disease is not modelled, and the goal of treatment is slowing down deterioration / progression. The cohort can enter the death state in any model cycle, with mortality risk derived from overall survival (OS) curves fitted to available intervention data from the respective clinical trials. Mortality risk is not health state dependent. The same model structure is used for both IPF and PPF, with different model input parameters according to the disease classification. The model structure is reproduced in Figure 8 below.

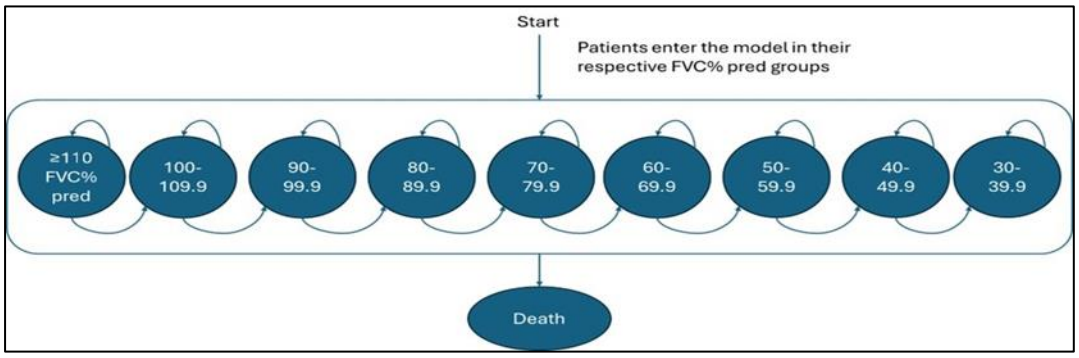


Figure 8 Company preferred Markov model structure (reproduced from Figure 34 of the company submission)

The EAG are satisfied that the company's model structure aligns with previous IPF/PPF NICE appraisals and FIBRONEER trial outcomes. The EAG note that lung transplantation is a potentially relevant outcome in this patient population, but that it was not included in the economic model structure. At clarification, the EAG

requested details of the numbers of lung transplantations across all interventions / comparators considered in the assessment, further justification for the exclusion of lung transplantation and a scenario analysis including a lung transplant state in the economic model. The company provided details of the numbers of lung transplants in the FIBRONEER trials (Table 15), and from real-world data, but did not provide any data from nintedanib or pirfenidone studies. The company also provided details from the NHS annual report on lung transplantation, the TRIPP study and details from their structured expert elicitation, all of which confirmed that the probability of lung transplantation was low amongst patients with fibrosis / ILD.

Table 15 Details of lung transplantation from FIBRONEER trials (re-produced from Table 5 of the company response to clarification queries)

	Nerandomilast 18 mg bid	Nerandomilast 9 mg bid	Placebo	Total
FIBRONEER-IPF				
Lung transplant in ES, n (%)	6 (1.5)	7 (1.8)	9 (2.3)	22 (1.9)
Lung transplant in monotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
FIBRONEER-ILD				
Lung transplant in ES, n (%)	10 (2.6)	3 (0.8)	10 (2.6)	23 (2.0)
Lung transplant in monotherapy, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: bid, twice a day; ES, entered set; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.
Sources: FIBRONEER-IPF CTR (Table 10.4); CSAP-137 (Table 47.1.1.1); FIBRONEER-ILD CTR (Table 10.5); CSAP-228 (Table 69.1.1.1).

The EAG accepts that the frequency of lung transplantation is low amongst fibrosis patients in the UK. The EAG notes that the company have provided data from the FIBRONEER trials only but have not provided information on lung transplantations amongst the relevant comparators (Nintedanib and Pirfenidone). Whilst the EAG acknowledges that the numbers of lung transplantations appear similar across the

nerandomilast and placebo arms of the FIBRONEER studies, it is feasible that any treatment effect might not be realised until longer into the future, for example when the cohort are more likely to have progressed into the lowest FVC % predicted model health state. A similar point would likely be relevant for nintedanib and pirfenidone. This could under-estimate the number of total lung transplants over the longer term across all treatment arms in the model. The EAG does consider the numbers of transplantations to be sufficiently high to have a major impact on the ICER. However, as the company correctly points out in response to clarification queries, the magnitude and direction of any bias due to the omission of a lung transplant state is unclear. That is because it is unclear to what extent the additional transplant costs would likely be associated with improvements in QoL, reduction in mortality risk. The direction of bias might depend on whether lung transplantation could allow cessation of anti-fibrotic treatments post-transplant, and to what extent the underlying cause of disease would be addressed through transplantation. The EAG's clinical expert is of the view that, only in some cases, would the course of ILD disease be altered following lung transplant and they do not envisage that any of the treatments under consideration would meaningfully alter the probability of patients receiving LT, with the requirement based more on underlying disease than a treatment effect of different anti-fibrotic. On balance, the EAG notes the omission of a lung transplantation state to be an area of unresolved uncertainty but considered the company's approach to be appropriate given the data available. The EAG also note that any scenarios that are not evidence-based risk introducing further bias in the cost-effectiveness results and therefore, on reflection, the EAG are satisfied with the company's decision not to include a scenario with a lung-transplant state added to the model.

4.2.3 Population

The modelled patient population is adults with IPF or PPF, with model baseline characteristics derived from the patient characteristics for Age, Gender and starting health state distribution as reported in the FIBRONEER-IPF and FIBRONEER-ILD studies for IPF and PPF respectively. The baseline characteristics of the population are summarised in Table 16.

Table 16 Model baseline characteristics, including starting health state distribution for IPF and PPF.

Variable	IPF	PPF
Age, mean (SD)	70.4 (0.5)	66.2 (0.4)
Male, n (%)	262 (76.0%)	662 (49.8%)
Health state starting distribution in the economic model		
≥ 110	[redacted]	[redacted]
100–109.9	[redacted]	[redacted]
90–99.9	[redacted]	[redacted]
80–89.9	[redacted]	[redacted]
70–79.9	[redacted]	[redacted]
60–69.9	[redacted]	[redacted]
50–59.9	[redacted]	[redacted]
40–49.9	[redacted]	[redacted]
30–39.9	[redacted]	[redacted]

The EAG are satisfied that the participant characteristics from the FIBRONEER studies are broadly aligned with the patient characteristics that would be most likely to receive nerandomilast in UK clinical practice, and so are appropriate for defining the model base case cohort.

4.2.4 Interventions and comparators

The intervention is nerandomilast 18mg, used as a monotherapy (as described in Table 2 of the company submission). For IPF, the comparators are nintedanib, pirfenidone and BSC. For PPF, the comparators are nintedanib and BSC.

The EAG raises the following points for consideration:

1) *Concomitant medications are not considered. In response to clarification queries, the company justified this on the grounds that inclusion of concomitant medication costs from the clinical trials would not impact*

substantially on the ICER because they were similar across groups. Whilst the EAG would have preferred for concomitant medications to be included, the EAG accepts the company's rationale and note that the impact on the ICER would be unlikely to be large.

2) *The EAG note that, for IPF, pirfenidone is only recommended for a cohort of IPF patients who have a baseline predicted FVC % predicted of 50%-80%. The EAG note that this accounts for only [redacted] of the modelled IPF cohort. This raises questions about the extent to which the pirfenidone trial data can be robustly compared to nintedanib or nerandomilast without adjustment for baseline FVC % predicted.*

4.2.5 Treatment effectiveness and extrapolation

Baseline FVC % predicted health state transition probabilities.

Health-state transitions were estimated using Poisson regression using patient level data from the FIBRONEER trials for both IPF and PPF. The models counted each additional 10% decline in FVC % predicted from baseline as an event. The company note that logistic regression based on previous NICE appraisals provided results that lacked face validity when applied to the FIBRONEER data. This was because initial improvements for nerandomilast were subsequently classed as progression events, despite no reduction from baseline haven occurred. Additionally, the company noted that there was substantial short term measurement noise, which added uncertainty. Instead, the Poisson regression models measure all declines relative to baseline, reducing the influence of short-term measurement noise. The base case model then assumes that the rate of decline above and below the median FVC % predicted of ~80% are different, with slightly lower rate of decline amongst the lowest health states.

The EAG considers the company's approach of using a Poisson regression model to be reasonable. Poisson regression avoids the issues identified by the company by measuring all declines relative to baseline, reducing noise and preventing treatments with early improvements from being unfairly penalised. It also captures all decline events, increases statistical power, and aligns with observed trial outcomes. The EAG also accepts that the use of Poisson regression modelling to estimate transition

probabilities has a precedent from previous NICE appraisals (see for example TA 984)[28] and is a relevant consideration in NICE DSU TSD 2, where logistic regression might be considered inappropriate.[29] Whilst the EAG agrees with the company's approach, it would still have been helpful to see if the company provided the results of the logistic regression modelling to validate the limitations and provide reassurance that these limitations have been successfully addressed by moving to a Poisson model. The EAG's view is that the company's adjustment to reduce transition probabilities between health states <80% FVC predicted is reasonable and that a slightly slower rate of decline has clinical face validity.

Relative treatment effects in FVC % predicted

The company applies a constant probability of FVC % predicted decline (>10%) per cycle, derived from the Poisson regression model detailed above. The company then assume, due to a lack of a consistent treatment effect between different FVC % predicted health states that the transition rates probabilities between health states are equal across all active treatment arms, for both IPF (Nintedanib, Nerandomilast and Pirfenidone) and PPF (Nintedanib and Nerandomilast). Scenario analyses use the estimates from the meta-regression for nintedanib (IPF and PPF) and from the NMA for pirfenidone (PPF). The company conduct additional scenario analyses applying a disease acceleration factor following acute exacerbation from external evidence.

The company's preferred modelling assumptions imply that none of the incremental QALY gains for nerandomilast vs. comparators are derived from reductions in the risk of decline in FVC % predicted. The EAG notes that alternative estimates are available from the NMR and NMA. The NMR shows substantial uncertainty, but with point estimates of treatment effect size suggesting a slower rate of decline for nintedanib compared to nerandomilast on average, and similarly the NMA shows a slower rate of decline on average for pirfenidone compared to nerandomilast. The EAG considers the company preferred base case assumption to generate a small bias in favour of nerandomilast in the economic modelling. The EAG accepts however that the treatment effect estimates from both the NMR and NMA analyses are highly uncertain, as evidenced from wide confidence intervals for all treatment effect sizes for progression in FVC % predicted. The EAG consider it unusual to

implement an assumption of equivalence, with certainty, when alternative data could have been used instead. The EAG would have preferred for this uncertainty to be incorporated directly into the probabilistic analyses to illustrate the impact of that uncertainty for decision making. The EAG therefore considers it more appropriate to make the best use of the available data, using the results from the meta-regression and NMA for the base case analysis. The EAG does not consider the company's scenario analysis applying an accelerated disease progression modification following acute exacerbation to be appropriate as acute exacerbations are already accounted for in the base case model of disease progression rates derived from the Poisson models. Company and EAG preferred transition probability assumptions are compared in Table 17 below.

It should be noted though that ICERs for nintedanib vs pirfenidone for IPF should not be interpreted because they rely on pairwise comparisons vs. nerandomilast that utilise different methods and measures of relative treatment effect. When considering a fully incremental analysis across all treatments (nerandomilast, nintedanib and pirfenidone), the EAG notes that the use of ORs for all comparisons, derived from the NMA may be a suitable alternative approach.

Table 17 Comparison of Company and EAG preferred baseline and relative treatment effects on FVC% predicted.

Parameter	IPF		PPF	
	Company preferred	**EAG preferred**	**Company preferred**	**EAG preferred**
Nerandomilast	FVC% predicted ≥80%, [redacted] decline per cycle, FVC % predicted <80%, [redacted] decline per cycle.	As per company base case	FVC% predicted ≥70%, [redacted] decline per cycle, FVC% predicted <70%, [redacted] decline per cycle.	As per company base case
Nerandomilast vs. Nintedanib.	Assumed equivalent	Base case, rate ratio from NMR: [redacted]; Scenario analysis, OR from NMA: [redacted].	Assumed equivalent	Rate ratio applied from the NMR: [redacted]
Nerandomilast vs. Pirfenidone.	Assumed equivalent	Base case, apply OR from NMA: [redacted] [redacted][A]	N/A	N/A
BSC.	FVC% predicted ≥80%, [redacted] decline per cycle, FVC% predicted <80%, [redacted] decline per cycle.	As per company base case	FVC% predicted ≥70%, [redacted] decline per cycle, FVC% predicted <70%, [redacted] decline per cycle.	As per company base case

***Note:** [A] Note that the company has incorrectly applied a OR for PFN vs. NERA 9mg for this scenario analysis, rather than the OR for PFN vs. NERA 18mg. Company scenario uses OR: [redacted]; Correct value (as per the company's NMA report, Figure 5, page 30) is [redacted].

Abbreviations: BSC, best supportive care; FVC, forced vital capacity; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis; N/A, not applicable; NMA, network meta-analysis; NMR, network meta-regression; OR, odds ratio; PPF, progressive pulmonary fibrosis.

Overall survival

The risk of mortality in any given cycle is modelled as being treatment dependent, rather than health state dependent, or being directly related to relevant clinical events like acute exacerbations. In the company preferred base case analysis, long-term mortality for Nerandomilast 18mg and Nintedanib was based on joint survival models using the individual-patient data (IPD) from the FIBRONEER, pooled with INPULSIS (IPF) or INBUILD (PPF) trial data. The joint survival models included only treatment arm as a predictor and were used to estimate a HR of treatment effect on mortality (HRs. vs. a baseline curve for nerandomilast). A scenario analysis used a model that included both treatment arm and history of acute exacerbations as predictor variables.

The company chose joint models because they assumed that the proportional hazards (PH) assumption holds for both IPF and PPF, and that HRs derived from the joint models were therefore appropriate for informing the economic model. The company noted that joint models are advantageous because they allow direct estimation of treatment effects, maintain internal validity, preserve randomisation, and align with clinical expectations. The assessment of the PH assumption was based on the company's interpretation of Schoenfeld residual plots, global and individual (by treatment arm) PH tests, visual inspection of log cumulative hazards plots and clinical expert validation (See appendix M.3.1 and M.3.2 of the company submission for IPF and PPF respectively). Whilst the company note that the tests show violation of the PH assumption for nintedanib for IPF, the company consider this not to be sufficient grounds to reject the PH assumption. The company justify their conclusion on the grounds that the apparent violation of the assumptions could be explained as an artefact of small event numbers in the FIBRONEER study for Nerandomilast (N=3) and Placebo (N=12), recorded over [redacted] and [redacted] years of follow-up for nerandomilast and placebo respectively. There was less uncertainty about the appropriateness of the PH assumption for PPF. Independently fitted models were not presented in the company submission or economic model and time dependent HRs were not considered. The company justified the use of joint, rather than independent curves on the grounds that the PH assumption was found to hold true and that there was potential for independently fitted curves to provide

implausible combinations of outcomes across treatment arms (e.g. BSC with better OS outcomes compared to active treatments).

A range of different overall survival (OS) parametric extrapolation curves (Exponential, Gompertz, Gamma, Weibull, Log Normal, Log-Logistic and Generalised Gamma) were considered for the joint models. The Generalised gamma model failed to converge for IPF and was therefore excluded from consideration. Curve assessment followed the recommendations of NICE DSU TSD 14.[30] All curves provided reasonable fit to the KM data and broadly similar AIC / BIC scores (See Section 3.3.3.1.3 and 3.3.3.2.3 of the company submission for IPF and PPF respectively). The company chose the gamma curve as their preferred extrapolation for both IPF and PPF, primarily based on clinical expert validation against expectations for nerandomilast, nintedanib, and BSC.

For Pirfenidone, individual-patient level data were not available to the company for analysis. The company therefore assumed that pirfenidone mortality was equal to that of nintedanib, with a scenario analysis exploring the impact of applying HRs for time to death, obtained from the Bayesian NMA (for PFN vs. Nerandomilast) ITC. The company justified their preference for an assumption of equivalence, over the ITC data, on the grounds that this aligns with the NICE committee decision from TA379, clinical validation, and risk of bias when using aggregate data.

The EAG raise the following points of critique regarding the company's preferred approach to modelling overall survival.

1) *The EAG notes that assuming treatment specific OS, rather than health state specific mortality risks adds some uncertainty to the overall life year gains in the model as the risks of mortality are not directly linked to the clinical events and health state that are most likely to lead to mortality. However, in the absence of sufficient data to populate excess mortality risks by health state, the EAG considers the company's approach to be reasonable. However, it would have been reassuring if the company provided any available data illustrating the impact of FVC% predicted health state on mortality using data from the studies (e.g. providing the last measured FVC% predicted amongst those who subsequently died in the trials).*

2) *The EAG agrees that the IPD analysis is the most appropriate source of data for modelling Nerandomilast, Nintedanib and BSC for both IPF and PPF. The EAG also agrees that the PH assumption is likely to hold for PPF and that joint survival models are appropriate. However, the EAG is less convinced that the PH assumption holds for IPF. As noted by the company, the global test ($p<0.05$), individual test for nintedanib ($p<0.05$) and the log-cumulative hazard plots (showing crossing curves) all point towards violation of the PH assumption. The company justify retaining the assumption because of small event numbers; however, this does not provide adequate evidence to support the PH assumption. The EAG are of the view that low-event numbers creates uncertainty and that assuming PH holds true may be less appropriate in such a scenario, especially when the available diagnostics suggest violation. The EAG note the company's explanation that individually fitted curves were excluded because of implausible crossing of the BSC and active treatment curves. However, it was not clear to the EAG if this was the case for all combinations of extrapolation curves that could have been fitted to the respective treatment arms. The EAG also note that individually fitted curves were not available within the economic model. Furthermore, the EAG note that alternative statistical methods, such as analysis models investigating time dependent HRs could have been considered. The magnitude and direction of any potential biases are therefore unclear. Given the data available from the company submission, the EAG aligns with the joint modelling approach for Nerandomilast, Nintedanib and BSC, acknowledging the advantages of having IPD analyses, retaining benefits of randomisation in a single model and the internal validity it provides. However, the EAG would have liked to see sensitivity analyses using independently fitted curves to explore the impact on the ICER for IPF.*

3) *The EAG are generally satisfied that the company's approach to selecting an appropriate OS curve, given the available data, is reasonable and is aligned with expectations of the EAG's clinical expert.*

4) *For the IPF comparisons involving pirfenidone, the EAG accepts that the company's assumption of equivalence appears to be broadly validated by*

similar effect size estimates of the HR for nerandomilast 18mg vs. NDB and nerandomilast 18mg vs. PFN from the NMA. However, the EAG also notes that the confidence intervals surrounding the effect sizes are wide, illustrating substantial uncertainty about the true effect size. The EAG is therefore of the view that assuming numerical equivalence under-estimates the uncertainty surrounding effect sizes in the probabilistic analysis. The EAG therefore prefers to use the best available data for the comparison, which are the HRs from the Bayesian NMA for the comparison of nerandomilast 18mg vs. PFN. Whilst the EAG notes the company's concerns about biases in the Bayesian NMA, the EAG's clinical expert did not consider the trials to be sufficiently different to such an extent as to conclude that the NMA was not robust. Furthermore, the company has not provided a detailed assessment of the trial characteristics that would preclude the use of the NMA in the economic model for mortality outcomes. Indeed, the EAG are of the view that the NMA findings broadly support an assumption of equivalence but note that the uncertainty surrounding that assessment should be included in the model.

During the assessment period for this appraisal, the company provided an addendum to their company submission post clarification phase to correct an error identified where the post clarification version of the economic model included a HR for NERA 18mg vs. NDB that was obtained from an older version of the company's NMR analysis. This was subsequently updated in the company addendum, and the corrected values are provided in the analyses that follow. The EAG has reviewed the NMR inputs to the model for mortality and is satisfied that the mortality inputs are now aligned with the most recent version of the NMR report.

A summary of company and EAG preferred base case overall survival assumptions is provided in Table 18 below. Company and EAG preferred mortality curves for IPF are compared in Figure 9 which shows that company and EAG preferred curves are aligned for NDB and NERA, and only slightly different for PFN. Figure 10 illustrates the preferred mortality curves for PPF, noting that company and EAG preferred preferences given the available data are aligned.

Table 18 Company and EAG preferred base case mortality assumptions

Parameter / Assumption	IPF		PPF	
	Company Preferred	**EAG preferred**	**Company preferred**	**EAG preferred**
Nerandomilast 18mg & BSC arms	FIBRONEER-IPF trial data	As per company base case	FIBRONEER-ILD trial data	As per company base case
Nerandomilast 18mg vs. Nintedanib	HR from NMR: [redacted]	HR from NMR (as per company base case). [redacted] Considers a scenario analysis, HR from NMA to maintain consistency of methodology across all active treatment comparisons: [redacted]	HR from NMR: [redacted] [A]	As per company base case
Nerandomilast 18mg vs. Pirfenidone	PFN assumed equal to NDB	HR from NMA: [redacted]	Not Applicable	Not Applicable
Survival modelling approach to curve selection for pooled data analysis for NMR.	Joint models, assumes PH assumption holds.	Unclear if PH assumption holds; aligns with company for base case but would have preferred scenario analyses using independently fitted survival curves.	Joint models	Joint models
Survival curve	Gamma	Gamma	Gamma	Gamma

Notes: [A] The company submitted model post clarification queries contained an error in the input parameter for the HR of NERA18mg vs. NDB for PPF, where results from an older version of the analysis were applied. The originally submitted HR (NERA18mg vs. NDB): [redacted] was subsequently corrected by the company in an addendum and is also updated in all analyses in the EAG report.

Abbreviations: BSC, best supportive care; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib, NERA, nerandomilast 18mg; NMA, network meta-analysis (Bayesian); NMR, network meta-regression; PH, proportional hazards; PPF, progressive pulmonary fibrosis.



Figure 9 Comparison of company and EAG preferred overall survival curves (IPF).



Figure 10 Company and EAG preferred overall survival curves.

Risk of acute exacerbations

The risk of acute exacerbations in the economic model is treatment specific and is not assumed to be health state dependent in the base case analysis. The company preferred approach follows a similar process as described for mortality above. Briefly, the company preferred risks of acute exacerbation were derived by:

1) Using pooled data across FIBRONEER-IPF and, INPULSIS (for IPF) and the pooled data across FIBRONEER-ILD and INBUILD (for PPF) to derive acute exacerbation risk per cycle for nerandomilast and BSC.

2) Applying treatment effects for nintedanib vs. nerandomilast 18mg based on the IPD NMR, using joint models with a covariate for treatment effect only. An exponential distribution was chosen, assuming that the PH assumption holds. The company has provided a full assessment of the PH assumption (global, individual tests, Schoenfeld residual plots and log-cumulative hazards plots) in Appendix M.4.1 and M.4.2 for IPF and PPF respectively.

3) For pirfenidone (IPF only), assuming that the risk of acute exacerbation in each model cycle was equal to that of nintedanib.

Two scenario analyses were conducted: a) assuming all active treatment arms have the same risk of acute exacerbation (assumed equal to nerandomilast) and b) where an additional risk of acute exacerbation was applied as FVC% predicted reduced, in addition to the modelled treatment effect, reflecting clinical expert opinion that lower FVC% predicted increases the risk of acute exacerbation.

The EAG raise the following points of critique for the methods to derive the proportion of patients experiencing acute exacerbations by treatment arm in each model cycle.

1) Acute exacerbation events are based on extrapolations of evidence from the respective trials rather than by health state. The company explores adding an acceleration factor for disease progression amongst those experiencing an acute exacerbation. In response to a clarification query requesting further details of the link, and evidence to support increasing risk of acute

exacerbation by health state, the company provided additional data from FIBRONEER, INPULSIS and INBUILD which verifies an increasing trend of acute exacerbations by health state, although there is insufficient evidence to support a treatment arm effect separately by health state due to small event numbers (See Tables 7-10 of the company's response to clarification queries). Whilst the EAG notes the increasing trend of acute exacerbations with disease progression, it would not be appropriate to include independent treatment and health state effects in the model, due to a risk of double counting. Furthermore, given that the company has chosen to assume equivalent health state transition probabilities across active treatment arms in their base case, the EAG considers the approach of applying a treatment effect that is constant across all health states to be a reasonable alternative approach, given the available data.

2) *The EAG is satisfied that pooling of data from FIBRONEER and INPULSIS (IPF) or INBUILD (PPF) trials is appropriate and makes best use of the available individual-patient data. The EAG is generally satisfied, based on the diagnostic assessments provided in Appendix M, that the PH assumption is reasonable for acute exacerbations for both IPF and PPF. Whilst an exponential curve seems to be well justified, the EAG notes that it is not possible to explore uncertainty around the chosen extrapolation curve in the company's economic model, meaning this remains an area of residual unresolved uncertainty. The likely magnitude of any bias by selecting the wrong PH curve is likely to be small, given that the HRs for Weibull, Gompertz and Exponential curves are all broadly similar (See Appendix M.4.1, Table 88 and Appendix M.4.2, Table 92 for estimated HRs for IPF and PPF respectively). The EAG would welcome the opportunity to explore the impact of different chosen survival curves for acute exacerbation on the ICER but are satisfied that the company's approach of using joint models with an exponential distribution is a reasonable conclusion given the data provided.*

3) *The EAG notes that the company have not used a competing risks model to estimate any of their treatment effect sizes and that competing risks have not been accounted for in the economic modelling. This likely biases results as*

death is likely to be a competing risk for people experiencing acute exacerbations. The magnitude of any bias depends on the underlying numbers of events in the respective studies. See Section 3.3 for the EAG's critique of the lack of a competing risks model. The EAG are of the view that a competing risks model could have been used to inform the economic model by providing HRs of acute exacerbation that more appropriately account for the competing risk of death. This remains an area of residual uncertainty for decision making.

4) *The EAG does not consider the assumption of equivalence in the risk of acute exacerbations between PFN and NDB for IPF to be based on robust evidence. However, the EAG also notes that it would not have been possible to estimate a HR of acute exacerbations for pirfenidone from the available trial evidence due to a lack of reporting of time to event for this outcome in the pirfenidone trials.[31-33] It was therefore not possible to include it in the NMA. Instead, an odds ratio, based on available acute exacerbations data from the trials at 52 weeks, was available from the Bayesian NMA for Nerandomilast vs. PFN. The EAG accepts that it would not be appropriate to combine HRs and ORs for different treatments in a fully incremental cost-effectiveness analysis (i.e. for NERA18mg, NDB and PFN for IPF), but notes that for the pairwise comparison of PFN vs. NERA, the use of an OR from the NMA would be appropriate. The EAG notes that an equivalent OR from the NMA for NDB vs. NERA was not provided by the company in the economic model, therefore it was not possible to provide the EAG's preferred approach for the fully incremental analysis.*

Company and EAG preferred assumptions for the risk of acute exacerbations are summarised in Table 19 below.

Table 19 Company and EAG preferred acute exacerbations assumptions

Parameter / Assumption	IPF		PPF	
	Company Preferred	**EAG preferred**	**Company preferred**	**EAG preferred**
Statistical approach for comparison	HRs from NMR for Nera 18mg vs. NDB [redacted] PFN assumed equal to NDB	As per company base case OR from NMA for Nera 18mg vs. PFN: [redacted] For fully incremental analysis, EAG would have preferred OR from Bayesian NMA for all comparisons, but these effect sizes were not available.	HRs from NMR for NDB vs. NERA; [redacted]	HRs from NMR NDB vs. NERA; [redacted]
Survival modelling approach	Joint models, assumes PH holds, apply exponential.	Accepts PH likely to hold, exponential well justified, but would have appreciated scenario analyses using alternative curves.	Joint models, assumes PH holds, apply exponential	Accepts PH likely to hold, exponential well justified, but would have appreciated scenario analyses using alternative curves.

Abbreviations: HR, hazard ratio; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib, NERA, nerandomilast 18mg; NMA, network meta-analysis (Bayesian); NMR, network meta-regression; OR, odds ratio; PH, proportional hazards; PPF, progressive pulmonary fibrosis.

Treatment sequencing:

The company assumes a simplifying modelling approach and does not consider treatment sequencing. Nerandomilast, and all other active comparators are assumed therefore to be used as monotherapies, followed by BSC after discontinuation. The company's justification is that there is insufficient evidence to populate the economic model with effectiveness or cost data for further lines of treatment following discontinuation. However, the company submission notes that treatment sequences may be considered in UK clinical practice.

The EAG considers this to be an important area of discrepancy between the economic model structure and real-world clinical practice. The EAG's clinical expert, aligned with the company sought expert opinion, is that UK clinicians would want to provide alternative AF treatments post nerandomilast discontinuation. The company's clinical expert opinion also noted that they would also prefer to have access to nerandomilast as a subsequent treatment post alternative AF therapy.

The EAG's clinical expert explains that the mechanisms of action for Nintedanib and Pirfenidone are different to nerandomilast and it is plausible that some treatment benefit might be attained from those treatments, even amongst people who have previously progressed on nerandomilast treatment. On the other hand, the EAG also accepts that it is unlikely that a treatment would have equal effectiveness at second line as it would have had at first line, and it is reasonable to assume that people having progressed on nerandomilast might have disease that is more difficult to treat. The EAG notes that the magnitude of any bias associated with excluding second line treatments is unclear and depends on the relative additional costs and benefits of subsequent lines of treatment. The EAG note that including subsequent treatments would increase treatment acquisition costs. The magnitude of increase in costs in the pathway would depend on the treatments used at 2nd line (nintedanib or pirfenidone). However, the increase would be higher in the nerandomilast arm of the model, due to the availability of more treatment options, especially for IPF (where NDB and PFN would both be feasible subsequent treatments). The magnitude of any bias on the ICER would then depend on the magnitude of QALY gain derived from any additional effectiveness on mortality reduction, acute exacerbation reduction and disease progression that might be achievable as subsequent

treatment. The EAG considers this to be an unresolved area of residual uncertainty for decision making that could have an important impact on the ICER. The EAG would have welcomed scenario analyses that explored the impact of subsequent treatment lines on cost-effectiveness results, even if those scenarios might be surrounded by considerable uncertainty, particularly about effectiveness parameters.

Treatment discontinuation curves:

For Nerandomilast and Nintedanib, the base case analysis applies a constant rate of treatment discontinuation per cycle, based on the available trial data over follow up for the FIBRONEER-IPF and ILD studies (Nerandomilast) and from the INPULSIS (IPF) or INBUILD (PPF) data for Nintedanib. The base case approach uses the raw data from the respective clinical studies, assuming an exponential rate of discontinuation for all treatments. Scenario analyses are available within the company's submitted economic model to:

1) apply HRs from the NMR for treatment discontinuation for NDB and NERA to be estimated using the pooled IPD data from the FIBRONEER-IPF and INPULSIS (IPF) and from FIBRONEER-ILD and INBUILD (PPF). This approach assumes that the PH assumption holds for treatment discontinuation and that HRs estimated from the joint models (i.e. The NMR) can be used.

2) Apply treatment independent parametric discontinuation curves (time to treatment discontinuation, TTD), fitted to data from the respective clinical trials. A range of treatment independent curves are available (exponential, Weibull, Gompertz, gamma, log-logistic and log-normal). Generalised gamma was tested but failed to converge for both populations. Further details of the company's approach to curve selection for the independent parametric survival analyses are provided in Appendix M of the company submission. KM curves for treatment discontinuation are provided in Figures 43 and 45 of the company submission for IPF and PPF respectively.

The EAG note that treatment discontinuation rates per cycle are substantially higher for NDB than for NERA for both IPF and PPF sub-populations. This leads to lower treatment acquisition costs for nintedanib, especially given that that constant

discontinuation rates are projected to extend over the lifetime horizon of the economic model.

The EAG has inspected the PH diagnostics provided by the company in Appendix M.5.1 (IPF) and M.5.2 (PPF). Based on statistical analyses of cox models with interactions between the HR and time or log-time, inspection of log cumulative hazards plots and Schoenfeld residual plots and tests, the EAG agrees with the company's assessment that the PH assumption appears to hold true for IPF (NDB and NERA). All diagnostics except the global Schoenfeld test also show a lack of evidence to reject the PH assumption for PPF. On this basis, the EAG concludes that the PH assumption seems reasonable for treatment discontinuation for NERA and NDB for both IPF and PPF. As the NMR maintains benefits of randomisation across studies and utilises the best available data, the EAG prefers to use a HR for NDB vs. NERA as the preferred base case scenario for treatment discontinuation in both IPF and PPF. The EAG notes that it was only possible to apply HRs to a baseline constant rate of discontinuation for nerandomilast, assuming an exponential distribution. It was not possible to apply HRs from alternative parametric survival extrapolations (e.g. Gompertz), but it was possible to apply these independently to each treatment arm.

The EAG notes that, in the scenario analyses utilising treatment independent survival extrapolation curves, that the Gompertz appears to be the PH compliant curve with the best fit to the underlying data for IPF (Table 96 and 98 Appendix M of the company submission). An exponential (NERA) or Weibull (NDB) appears to provide the best fit for PPF. The EAG and company conclusions regarding the most appropriate curves are therefore aligned for scenarios applying independent survival curves for treatment discontinuation. Whilst the choice of preferred independently fitted curve are aligned, the EAG noted substantial differences between the extrapolations reported in Appendix M of the company submission and those provided within the treatment discontinuation tab of the company's economic model. Following an additional request from the EAG, the company subsequently provided an addendum to their submission with corrected curves for Appendix M. The company confirmed that the data included in the economic model were correct and that the Appendix M extrapolation curves were a reporting error. However, as

independently fitted treatment discontinuation curves do not part of the EAG's or company's preferred base case, the EAG does not consider these independently fitted curves further.

As with acute exacerbations and mortality parameters, the EAG disagrees with the assumption that PFN treatment discontinuation is equal to NDB for IPF. Instead, the EAG prefers to apply the OR from the Bayesian NMA, with the already noted caveats around mixing effect size measurements (OR and HR) for the fully incremental cost-effectiveness analysis. For the fully incremental analysis, the EAG considers ORs from the NMA for all comparisons to be a plausible alternative data source.

Company and EAG preferred treatment discontinuation assumptions are compared in Table 20 and resulting discontinuation curves for IPF are compared in Figure 11.



Figure 11 Comparison of company and EAG preferred treatment discontinuation curves (IPF).

**Note: Company preferred NDB and EAG preferred PFN curves seem very similar but are slightly different numerically.*

Table 20 Company and EAG preferred treatment discontinuation assumptions

Parameter / Assumption	IPF		PPF	
	Company Preferred	**EAG preferred**	**Company preferred**	**EAG preferred**
Preferred approach: NERA	constant rate (exponential) from FIBRONEER-IPF trial data: [redacted] per cycle	As per company base case	constant rate from FIBRONEER-ILD trial data: [redacted] per cycle	As per company base case
Preferred approach: NDB	constant rate (exponential) from INPULSIS trial data: [redacted] per cycle	Apply HR from NMR for Nera 18mg vs. NDB: [redacted][A]; Scenario analysis to use the OR from the NMA for NERA 18mg vs. NDB: [redacted]	constant rate (exponential) from INBUILD trial data: [redacted] per cycle	Apply HR from NMR vs. NERA 18mg: [redacted]
Preferred approach: PFN	Assume equal to NDB: [redacted] per cycle	Apply OR from NMA NERA 18mg vs. PFN: [redacted]	N/A	N/A

Abbreviations: HR, hazard ratio; N/A, Not Applicable; NERA 18mg, Nerandomilast 18mg; NDB, nintedanib; NMA, network meta-analysis; NMR, network meta-regression; OR, odds ratio; PFN, pirfenidone.

Notes: [A] The company submitted model post clarification queries contained an error in the input parameter for the HR of NERA18mg vs. NDB for IPF, where results from an older version of the analysis were applied. The originally submitted HR for time to treatment discontinuation (NERA18mg vs. NDB): [redacted] was subsequently corrected in the company revised addendum model, though the description of the change on page 2 of the addendum documentation appears incorrect for IPF. The EAG has cross checked the revised addendum model against the NMR report and is satisfied that the values included in the model, as reported in this table are correct.

Treatment Stopping Rule:

The company base case analysis applies a stopping rule for all active treatments, across both IPF and PPF. The stopping rule is applied when patients experience a greater than 10% absolute decline in FVC % predicted in any one state. Practically, in the economic model, this means that the proportion of the cohort transitioning into a lower health state in any given cycle stop treatment in the economic model. This is modelled independently of the treatment discontinuation rate described above. A scenario also explored the impact of nerandomilast being the only treatment to have a formal stopping rule.

The EAG's clinical expert raised two points of consideration with respect to stopping rules. The first was that, in practice clinical experts would usually stop treatment if there was evidence of a sustained reduction in FVC% predicted, however they raised concerns about deciding to do this after only 3 months (cycle duration in the economic model). The EAG also noted that previous stopping rules implemented in NICE technology appraisals (TA504 – Pirfenidone for IPF; TA379 – Nintedanib for IPF) suggested a 12-month time frame before stopping treatment. Without the use of tunnel states in the economic models, it is unclear to the EAG how these stopping rules were operationalised over 4 successive 3-monthly cycles. The second point raised by the EAG's clinical expert was that whilst FVC% predicted was important, it could fluctuate over time and was not the only consideration when deciding whether to continue or stop treatment, and clinicians would appreciate flexibility to use their best judgement and experience in identifying patients who had sustained lack of treatment benefits.

The EAG notes some variation in committee preferences for stopping rules in previous technology appraisals:

- *TA504 (Pirfenidone for IPF): stopping rule after 12 months of >10% FVC% predicted decline.*
- *TA379 (Nintedanib for IPF, fvc 50-80% predicted): recommended with a stopping rule after 12 months of >10% FVC % predicted decline.*

- *TA864 (Nintedanib for IPF; fvc >80% predicted): recommended, with no formal stopping rule applied.*

- *TA747 (Nintedanib for PPF): recommended with no formal stopping rule applied.*

The EAG's clinical expert noted that all anti-fibrotic treatments would be managed similarly in UK clinical practice, with treatment being stopped for sustained decline regardless of whether a formal stopping rule was recommended or not. From this respect, the company's approach to applying a consistent decision rule across treatments is reasonable. However, there is some uncertainty that the EAG feel should be further explored in scenario analyses. The EAG therefore aligns with the company's approach for the base case, but considers the following scenario analyses where:

- *All stopping rules are removed (as per TA747 and TA864), apart from Nerandomilast 18mg (aligned with the company's conducted scenario)*

- *Stopping rules are disease condition dependent, applied to PFN and NDB for IPF (as per TA504 and TA379), but removed for PPF for NDB (as per TA747).*

The EAG scenario analyses changing stopping rules are applied to a 3-month decline in FVC% predicted as the company's economic model, with 3-monthly markov cycles does not allow for consideration of 12-month sustained decline stopping rules. The EAG has not explored scenarios where the stopping rule for NERA 18mg is removed as this was not included in the company's value proposition. The EAG considers the application of a stopping rule for NERA 18mg to be reasonable. Table 21 summarises the alternative approaches for stopping rules applied in the EAG scenario analyses.

Table 21 Base case and scenario analyses for stopping rules applied in the economic model.

Treatment	IPF; Stopping rule (Y/N)			PPF; Stopping rule (Y/N)	
	NERA 18mg	NDB	PFN	NERA 18mg	NDB
Co and EAG base case	Y	Y	Y	Y	Y
Co. scenario	Y	N	N	Y	N
EAG scenario	Y	Y	Y	Y	N

Duration of continued treatment benefit over time

The company's base case model assumes that treatment effects (for mortality and FVC% predicted health state) are maintained for one year (4 model cycles) after the maximum duration of follow-up from the FIBRONEER trials. The continuing treatment effect is applied to all active treatment model arms for a total model duration of [redacted] years (i.e. [redacted] cycles) for IPF and [redacted] years (i.e. [redacted] cycles) for PPF following treatment initiation. After this point, transition probabilities between FVC% predicted states and mortality risk per cycle are switched to the BSC arm of the model. The switch is only applied to the proportion of the cohort who are off treatment. This effectively means that treatment discontinuation only impacts on treatment specific mortality or FVC% predicted health state outcomes after [redacted] (IPF) or [redacted] (PPF). No treatment waning is applied to the proportion of the cohort who remain on treatment over the model time horizon.

In response to clarification questions (QB6), the company explained that extrapolations of treatment effect estimates (e.g., for mortality) explicitly account for the impact of treatment discontinuation during the trial follow-up, but that continuing treatment benefits after discontinuation beyond this time point are uncertain. The company also pointed out that the continuing duration of any treatment effect after treatment discontinuation was uncertain but provided data on treatment half-life which was approximately 10-17 hours for Nera 18mg; 10-15 hours for nintedanib; and 2.4 hours for pirfenidone respectively. The EAG's clinical expert is of the view

that, given the short half-life of the treatments, any continued treatment benefit following discontinuation would likely be very short and that, given the company's assumption of no subsequent active treatments (see critique above), that treatment effectiveness parameters would likely quickly return to those of BSC.

Given this information, the EAG are of the view that a loss of treatment effect over time is a reasonable assumption and that some form of waning of treatment effect is appropriate for the economic model. However, there are some concerns with the approach taken by the company to implement the treatment waning effect. First, the EAG would have preferred to see a treatment waning effect that was linked to the point of treatment discontinuation, not treatment initiation. This could have been achieved by using tunnel states in the model if the company wished to explore longer-term assumptions about time to loss of treatment effect post discontinuation. Given the short half-life reported by the company, assuming that the cohort directly transfers to the BSC transition probabilities and treatment effectiveness estimates within one cycle after discontinuation would have been plausible.

This above approach has an advantage of aligning treatment effectiveness loss to the point of discontinuation but has a limitation that the survival curves for treatment effectiveness (most importantly mortality) and based on the full trial monotherapy population, and therefore already implicitly include some impact of treatment discontinuation on risk of death. A more appropriate, and in the EAG's view, less biased approach would have been to explore the impact of loss in treatment effect over time directly on the treatment effectiveness extrapolation curves. For example, the company could have explored scenario analyses where the hazard ratios for Nera 18mg vs. comparators converged to 1 over time in the extrapolation phase of the model, reflecting that the magnitude of treatment effect might not be sustained indefinitely. Alternatively, independently fitted survival curves to Nera 18mg and NDB could have been used to explore a reduction in the implied HR over longer-term model extrapolation. As the EAG does not have access to the underlying data from the company's IPD analysis, it was not possible to explore the impact of alternative treatment waning assumptions, including use of independently fitted survival curves, on the ICER.

Company preferred and EAG suggested alternative scenario analyses are summarised in Table 22 below.

Table 22 Company and EAG alternative scenarios about duration of continued treatment benefit for active AF treatments

Parameter / Assumption	Company approach
Company approach	Transition probabilities and mortality effect sizes switched from active treatment to BSC arm for 'off treatment' proportion of the cohort after [redacted] and [redacted] years post treatment initiation for IPF and PPF respectively (based on 1 year post end of follow up from FIBRONEER trials)
Company scenarios	Scenarios explored 5 and 50 years with the latter retaining treatment effectiveness for the whole cohort as per the projected extrapolation curves
EAG alternative scenario suggestion 1	As per company scenario, but apply adjustment directly to HRs for the full modelled cohort to allow convergence of survival curves over time.
EAG alternative scenario suggestion 2	Switch transitions to BSC immediately at the point of treatment discontinuation

Summary of clinical parameters used in the economic model.

The company's economic model includes treatment effectiveness parameters for health state transition probabilities, mortality and risk of acute exacerbation. Treatment discontinuation is modelled and the company model includes an approach to model treatment waning effects in the 'off treatment' cohort, based on time since treatment initiation. A stopping rule is applied to all active treatments where FVC% predicted declines >10% in any one cycle (i.e. any health state progression).

The key differences between the company and EAG preferred base case analyses with respect to clinical inputs are as follows:

- The company prefers equal transition probabilities between FVC% predicted health state for all active treatment arms, whereas the EAG prefers to make the best use of the available data and apply treatment dependent transition

probabilities based on the data available from the NMR (nintedanib for IPF and PPF) and NMA (pirfenidone for IPF).

- For mortality, the company assumes the PH assumption holds, and that a joint survival model, with treatment as a predictor, using pooled data (NMR) data is appropriate for the comparison of NDB vs. NERA. The EAG agrees that NMR data are appropriate but questions the validity of the PH assumption for IPF and would have valued independently fitted curves as scenario analyses. This could also have helped address EAG concerns regarding the company's preferred treatment effect waning approach. For IPF, the company prefers to assume equivalence between PFN and NDB, whereas the EAG prefers to use HRs from the Bayesian NMA. Company and EAG preferences are otherwise aligned for PPF where NMR data are used for the comparison of nerandomilast vs. nintedanib.

- For acute exacerbations, the company prefers to use HR from the NMR for NDB vs. NERA for both IPF and PPF, based on survival extrapolations assuming the PH assumption holds and an exponential curve is appropriate. For PFN (IPF only) the company assumes equivalence to NDB. The company and EAG preferences are aligned for NDB vs. NERA, but for IPF the EAG prefers to use ORs from the Bayesian NMA instead, noting however that it was not possible to identify outcomes based on similar effect size reporting for all three active comparators, raising uncertainties about the appropriateness of a fully incremental analysis using alternative effect size types (OR vs. HR).

- For treatment discontinuation, the company prefers to use a constant treatment discontinuation rate based on the available trial data for NDB. The EAG prefers to use the HRs from the NMR. For PFN for IPF, the company assumes equivalence to NDB, whereas the EAG prefers to use ORs based on 52-week data from the Bayesian NMA.

- The company prefers to apply treatment waning effects that are based on time since treatment initiation for the 'off treatment 'proportion of the cohort. The EAG would prefer a scenario where the cohort continue along the

estimated mortality curves, but that treatment effect waning should be considered explicitly within the selection of the most appropriate survival curves.

- The company apply a stopping rule for all active treatments. The EAG considers this appropriate but notes some inconsistency compared to previous NICE technology appraisals. Scenario analyses are presented to illustrate the impact of alternative stopping rules for IPF / PPF, aligned with specific recommendations in previous TAs on the ICER.

4.2.6 Health-related quality of life

The company's base case economic model predicts that nerandomilast leads to increased QALYs compared to all other comparators, through a combination of life year gains (mortality benefit) and quality of life (utility benefit). QALYs are accrued through health state utility values (HSUVs) for FVC% predicted states, utility decrements associated with acute exacerbation events (applied in each cycle to the proportion experiencing an exacerbation) and disutility associated with liver function tests and adverse events. However, because the company's base case analysis assumes equivalence of transition probabilities between active treatment comparators, the HSUVs attached to FVC% predicted health states do not impact on incremental QALYs for nerandomilast vs. active treatment comparators (nintedanib or pirfenidone for IPF, or nintedanib for PPF). Utilities for the economic model are primarily informed by IPD analysis from the pooled FIBRONEER-IPF and INPULSIS (IPF) and pooled FIBRONEER-ILD and INBUILD (PPF) studies. Scenario analyses explore the impact on QALYs and the ICER of alternative utilities sourced from literature reviews and previous NICE technology appraisals.

Systematic literature review for utilities

The company conducted a systematic literature review to identify studies published from January 2011 to September 2025 for utility and HRQoL in IPF and PPF. The search followed a PICOS framework. Fully published journal articles, clinical trial records and conference abstract from 2023-2025 were included. They restricted the search to English language publications and abstracts. The full inclusion/exclusion criteria are outlined in CS appendix E.2 table 32. Four cost effectiveness studies

that reported EQ-5D values by FVC% predicted category were identified. The utility values reported in the cost effectiveness study by Rinciog et al. are used by the company in a scenario analysis.[26] These values were also used in previous technology appraisals for nintedanib, TA 379 and TA 864.[11, 12]

The EAG considers the company's systematic review of utility studies to be comprehensive and identifies appropriate values for scenario analyses.

Health State Utility Values:

The FIBRONEER, INPULSIS and INBUILD trials all collected EQ-5D-5L data at baseline and 52 weeks follow up. Responses were mapped to the 3L version and UK general population norm utilities. For the base case analysis HSUVs were derived from regression analysis of pooled data from the FIBRONEER-IPF and INPULSIS trials (IPF) and pooled FIBRONEER-ILD and INBUILD trials (PPF). Data from FIBRONEER studies were for the no AF (i.e. monotherapy) sub-population, with nerandomilast and BSC arms pooled, and from INPULSIS and INBUILD, both of which reflected monotherapy or BSC.

HSUVs were derived from a linear regression, with a baseline utility parameter, specific terms for each 10% predicted FVC % predicted band, a covariate for history of acute exacerbation in the last 30 days and a covariate for history of acute exacerbation in the last 31+ days. The company noted that there were insufficient patient numbers with a FVC% predicted > 80% to derive meaningful health state dependent utility values by 10% FVC% predicted category. Therefore, the company pooled all data points with FVC% predicted > 80% together and assumed the same utility across the three highest FVC% predicted health states in the model.

For health states where FVC % predicted ≥ 80% for IPF, trial-based utility values were higher than that of the age and sex adjusted general population norms. The company therefore capped utility values at general population norms for all health states with an FVC % predicted ≥ 80, with health state specific decrements applied multiplicatively for all other health states against the reported HSUV for all FVC% predicted >80% health states. Further adjustments are applied to allow utilities to reduce over time as the cohort ages in line with age and sex specific general population utility norms. For PPF, reported health state values were lower than

general population norms, but the company still applied a general population adjustment, inflating the reported values upwards to the age and sex adjusted gen pop norm value. Tables 23 and 24 below detail the company base case and alternative plausible HSUVs for IPF and PPF respectively.

Table 23 Summary of alternative IPF HealthState Utility Values

FVC % predicted	Base case: Pooled FIBRONEER-IPF & INPULSIS; Gen pop, age 70 capped; adjusted for acute exacerbation history.	As per co. base case (uncapped)	FIBRONEER- IPF Trial only	INPULSIS Trial only	Pooled FIBRONEER-IPF & INPULSIS; Uncapped, no acute exacerbation history adjustment.
≥ 110	[redacted]	[redacted]	[redacted]	0.8380	[redacted]
100–109.9	[redacted]	[redacted]	[redacted]	0.8380	[redacted]
90–99.9	[redacted]	[redacted]	[redacted]	0.8380	[redacted]
80–89.9	[redacted]	[redacted]	[redacted]	0.8105	[redacted]
70–79.9	[redacted]	[redacted]	[redacted]	0.7800	[redacted]
60–69.9	[redacted]	[redacted]	[redacted]	0.7657	[redacted]
50–59.9	[redacted]	[redacted]	[redacted]	0.7387	[redacted]
40–49.9	[redacted]	[redacted]	[redacted]	0.6634	[redacted]
30–39.9	[redacted]	[redacted]	[redacted]	0.6634	[redacted]
Source	Excel model for IPF	Excel model for IPF	Table 16 Clarification response	Excel model for IPF	Table 23 company's clarification response

Abbreviations: FVC: Forced Vital Capacity; IPF: Idiopathic Pulmonary Disease.

Table 24 Summary of alternative PPF HealthState Utility Values

FVC % predicted	Base case: Pooled FIBRONEER-ILD & INBUILD; gen pop uplift, age 66; adjusted for acute exacerbation history. [A]	As per company base case (uncapped)	FIBRONEER ILD Trial only	INBUILD Trial only	Pooled FIBRONEER-ILD & INBUILD; Uncapped, no acute exacerbation history adjustment.
≥ 110	[redacted]	[redacted]	[redacted]	0.7521	[redacted]
100–109.9	[redacted]	[redacted]	[redacted]	0.7521	[redacted]
90–99.9	[redacted]	[redacted]	[redacted]	0.7287	[redacted]
80–89.9	[redacted]	[redacted]	[redacted]	0.7333	[redacted]
70–79.9	[redacted]	[redacted]	[redacted]	0.7242	[redacted]
60–69.9	[redacted]	[redacted]	[redacted]	0.6750	[redacted]
50–59.9	[redacted]	[redacted]	[redacted]	0.6453	[redacted]
40–49.9	[redacted]	[redacted]	[redacted]	0.6045	[redacted]
30–39.9	[redacted]	[redacted]	[redacted]	0.6045	[redacted]
Source	Excel model for PPF	Excel model for PPF	Table 16 company's clarification response	Excel model for PPF	Table 23 company's clarification response

Abbreviations: FVC: Forced Vital Capacity; ILD: Interstitial Lung Disease; PPF: Progressive Pulmonary Fibrosis.

[A] General population utility for the highest reported value health state uplifted to age and sex adjusted general population norms.

The EAG are satisfied that the populations investigated in the FIBRONEER IPF and FIBRONEER ILD and INPULSIS / INBUILD studies are for the most part representative of UK population of IPF and PPF patients. It is therefore appropriate to pool the datasets for utility estimation because doing so provides a greater number of datapoints to inform the utility regression models and provides more robust estimates for populating the economic model.

The EAG are also satisfied that the company's utility estimation approach is robust. Linear regression rather than repeated measures models is appropriate due to data only being available at baseline and week 52. The EAG are also satisfied that the company's approach to general population utility capping is appropriate for IPF, where reported utility values were above those of the age and sex adjusted general population norm. However, for PPF, the EAG note that general population capping is applied by inflating reported health state PPF values to the general population norm for the PPF cohort. The EAG does not consider this approach for PPF to be well justified, but notes that the impact on the ICER is minimal.

The EAG agrees that it was appropriate to use relative rather than absolute decrements for adjustment. The EAG also notes that utilities are age and sex adjusted for each subsequent cycle of the model as the cohort ages and the approach is aligned with the NICE reference case recommendations.

Acute exacerbations

The company has included a short-term disutility for acute exacerbations in their model for IPF an PPF. A disutility of [redacted] is applied in their base case for IPF and [redacted] in their base case for PPF. The duration of acute exacerbation disutility is assumed to be 4 weeks (one third of the cycle duration in which the acute exacerbation occurs), and the company divided the disutility value by three resulting in a disutility per cycle of [redacted] for IPF and [redacted] for PPF patients who experience and acute exacerbation. The disutility values for acute exacerbation are derived from the "history of acute exacerbation in the last 30 days" co-variate in the regression analysis applied to the pooled FIBRONEER-IPF plus INPULSIS trials for IPF, and pooled FIBRONEER-ILD plus INBUILD trials for PPF. The company noted that their clinical experts were concerned that the high utility following exacerbation might not represent UK clinical practice. To address this, the company explore the use of

disutility values from the INPULSIS trial only (0.1400) for IPF and INBUILD trial only (0.1668) for PPF in scenario analysis (also applied for 4 weeks). The company also noted that there is also likely to be a longer-term utility impact of acute exacerbation, however, this is captured when a patient experiences disease progression with a reduction in FVC % predicted and enters a health state with lower utility value.

The company recognised that acute exacerbations were defined and documented differently across trials. In the INPULSIS trial investigator reported and adjudicated committee reported disutilities were reported whereas the FIBRONEER trial used confirmed and suspected events without adjudication. Whilst this might suggest that the FIBRONEER trial data should be preferred, the company also acknowledged that there is significant uncertainty surrounding the impact of acute exacerbations on utility from the FIBRONEEER Trials. They explain that there was an insufficient number of observed events in both treatment arms in FIBRONEER-IPF ([redacted] events for nerandomilast and [redacted] events for BSC) and FIBRONEER-ILD ([redacted] events for nerandomilast and [redacted] events for BSC) to estimate robust utility values. This limited the ability to detect meaningful differences between treatment and placebo groups for both IPF and PPF cohorts.

The EAG note that there are pros and cons of using the pooled vs. FIBRONEER only data for estimating the utility decrement associated with acute exacerbations. The EAG agree with the company's noted uncertainties and consider the company's base case analysis to make the best use of the available data. The approach maintains consistency with the preferred data source for health state utility value estimation and treatment effectiveness modelling. Whilst the EAG considers the company's preferred base case approach to be appropriate, scenario analyses that use the FIBRONEER only trial data for both health state valuation and acute exacerbation decrements would help illustrate the impact of any potential uncertainty on the ICER.

The EAG considers it appropriate to apply an acute exacerbation disutility in the economic model. The EAG also notes that a similar approach was taken in technology appraisal 747 for nintedanib for PPF where a short-term disutility of -0.0556 was applied for a duration of one month following an acute exacerbation.

Whilst the EAG acknowledges that there may be long-term utility decrements associated with acute exacerbation and initiation of supplemental oxygen therapy, the magnitude of net utility benefit from supplemental oxygen therapy is unclear (i.e. treatment benefit vs. negative implications). Additionally, longer-term utility decrements are, at least partially, captured in the HSUVs for each FVC% predicted state. Therefore, the EAG are of the view that applying a utility decrement in the state in which the exacerbation occurs is appropriate and aligned with the evidence from the adjusted regression models. Any longer-term decrement in subsequent cycles would be difficult to model accurately and would risk double counting. The EAG therefore agree that the company's base case analysis approach of applying acute exacerbation disutility only in the cycle in which it occurs, but not applying further long-term decrements is appropriate.

The EAG note that the company's disutility for acute exacerbation is only applied for 4 weeks in the model cycle in which the acute exacerbation occurs. The EAG feels that the disutility derived from history of acute exacerbation in the last 30 days covariate represents the disutility experienced for the first 30 days following an acute exacerbation event and should not be scaled down. The EAG also notes that the company's regression models include covariates for both history of acute exacerbation in the preceding 30 days and 31+ days, both of which show significant utility decrements. The EAG's clinical expert is of the view that disutility associated with acute exacerbations may last longer than 30 days, would reflect the need for commencing supplemental oxygen therapy amongst patients in lower FVC% predicted states, and might also reflect gradual deterioration prior to the exacerbation occurring. The EAG therefore prefers to apply the entire disutility derived from history of acute exacerbation in the last 30 days covariate for the first month of the cycle.

The EAG noted that the requirement for supplemental oxygen therapy was substantially higher following acute exacerbations in lower FVC% predicted states than compared to higher FVC% predicted states. In clarification queries, the EAG questions whether it might be possible to apply health state dependent utility acute exacerbation utility decrements. In their response to clarification question B8, the

company performed an analysis which included an interaction term between FVC % predicted and history of acute exacerbation in their regression models, however this yielded statistically insignificant and counterintuitive results whereby higher health states predicted lower utility values following an acute exacerbation. The company attribute this to the limited observations of exacerbation events in the trials. The EAG appreciate the additional analysis conducted and agree with the company that it would not have been possible to apply a health state specific acute exacerbation disutility in the model given the limited available data.

Adverse events

The company include disutilities for Grade 3+ adverse events, occurring with a frequency of 5% or higher in the nerandomilast arm of the FIBRONEER trials. The company also include AEs of Grade 3+ that were included in previous NICE TAs for IPF and PPF.[12-14] The duration of adverse event disutilities is 4.35 weeks. These include cardiac events, pneumonia, diarrhoea, GI disorders (without diarrhoea), and photosensitivity reaction. Full details of adverse event disutilities are provided in Table 55 of the company submission.

The EAG are generally satisfied with the company's approach to integrating adverse event disutilities in the economic model. The EAG noted the following minor points between company and EAG preferred assumptions but note that the impact on the ICER of these changes is minimal:

Sources used for the disutility values of cardiac events, diarrhoea, GI disorders (without diarrhoea) and photosensitivity reaction were also used in previous technology appraisals for nintedanib, TA 864 and TA 379. The disutility value for pneumonia had been used in a previous technology appraisal for sodium zirconium cyclosilicate for the treatment of hyperkalaemia, TA599.[34] These values were previously accepted by the NICE committee. A one-month duration was the ERG's preferred assumption in TA 379 and TA 864 for adverse event disutility which was also validated by clinical experts at the time. However, the EAG note some minor inconsistencies in how the company has scaled down the disutility value for diarrhoea, GI disorders (without diarrhoea) and photosensitivity reaction as outlined below.

Diarrhoea: Disutility value associated with diarrhoea was sourced from TA864 which used a value reported by Rinciog et al. 2017. The disutility by Rinciog et al is – 0.0057 for a serious GI event and the company assumes half of this value for diarrhoea disutility (0.00285). The company scaled down this value to a weekly value of 0.0002 (I.e. 0.00285/13.04).

However, the 0.0057 value reported reflects one month of disutility and not one cycle. Therefore, the 0.00285 should have been divided by 4, which would result in a disutility of 0.0007 instead of 0.0002.

GI disorders (without diarrhoea): Disutility value is assumed to be the same as that for diarrhoea which has been described above.

Photosensitivity reaction: Derived from by Ara and Brazier.[35] The figure reported by Ara and Brazier is 0.082 under "skin complaints". This figure appears to have been scaled down to 0.0004.

It is not clear what assumption the company has made regarding the duration of a 0.082 disutility to scale this down to 0.0004. The company used the same source to obtain a disutility for cardiac events, and this was scaled down on the assumption that the reported value was of 52-week duration. If the same assumption is applied to photosensitivity reaction a scaled down value is 0.0015.

Table 25 below outlines the adverse event disutilities reported by the company and the EAG's preferred disutility values.

Table 25 Company and EAG preferred adverse event disutilities.

Adverse event	Original Source (12 m)	Value used in TA 379 / 864 (1m)	Company weekly value	EAG weekly value	Source
Cardiac	0.198	0.0165	0.0038	0.0038	TA864; Ara and Brazier, 2011
Pneumonia	0.0776	-	0.0388	0.0388	TA599; Sullivan et al., 2011
Diarrhoea / GI disorders	0.068	0.0057	0.0002	0.0007	TA864; Rinciog et al., 2017, assume half of a serious GI event disutility

Photo-sensitivity	0.082	-	0.0004	0.0015	TA864; Ara and Brazier, 2011

GI perforation:

Gastrointestinal perforation has not been included in the company's submission. However, it was included in technology appraisal TA 379 for nintedanib to treat IPF as it is a rare but serious adverse event associated with this drug. In the cost effectiveness analysis of Nintedanib for IPF by Rinciog et al., it is reported that:

"Clinical advice at the time indicated that [gastrointestinal perforation] deserves a special mention as an event, as it may be very different to the gastrointestinal events already captured in the model".

They report the risk per cycle as 0.08 for those receiving nintedanib, the disutility and cost per event are –0.0098 and £2352.99 respectively.[26] The EAG feels that GI perforation is worth adding to the model, although it is unlikely to alter the overall outcome of the results, its inclusion would ensure that all relevant risks associated with the comparators have been captured.

Liver Function Tests (LFT)

The company applied a disutility for LFT. The disutility applied is 0.008, sourced from appraisal TA 898 which reports the disutility associated with three IV infusions.[36] The company adjusted the value reported to reflect the disutility associated with one infusion (0.008) and assume that this would equate to the disutility associated with liver function tests.

Comment: The disutility applied seems implausible for several reasons. The value of 0.008 is more than twice the value assigned for cardiac event disutility which is likely to carry a greater disutility for patients than an LFT. Additionally, the disutility is derived from a study that reports IV infusion disutility. An IV infusion procedure is different to a LFT blood test. An infusion lasts 30 mins, once a week for four weeks. "[37-40] Nintedanib requires monthly liver tests for the first 3 months, followed by regular checks as clinically indicated – many centres recommend quarterly thereafter in the UK, pirfenidone requires monthly liver function monitoring for 6 months, followed by quarterly checks ". This is unlikely to have a comparative impact on a patient's QoL

as an IV infusion. Furthermore, the EAG commented on this in the appraisal of TA 898 that this disutility value for an IV infusion lacked face validity as it was more than double the disutility applied for pneumonia in their model. They also highlight that the source of this utility used a time trade off method which does not align with the NICE reference case. The company have addressed this in the clarification letter and argue that the disutility has not already been captured by the health state utilities, as these were derived from RCT data, which likely include a cohort of patients residing in urban areas with easier access to care. They argue that in a real world setting many patients would not live in urban areas and endure the added burden of regular LFT which maybe cumbersome for those living far from such facilities. However, it is not plausible that the disutility associated with an IV infusion can represent the disruption caused by regular liver function monitoring for these patients. Our preferred approach is to exclude this disutility. The company has incorporated an option to exclude LFT disutility in their model.

4.2.7 Resources and costs

Resource use review

The company conducted a systematic literature review to identify evidence on relevant costs, resource use and the cost effectiveness of treatments for IPF and PPF. Separate searches were performed for IPF and PPF. Studies from January 2014 to September 2025 were included. The quality of the studies was assessed by two reviewers, and any conflicts were resolved by a third reviewer. The Drummond check list was used to assess the quality of the economic evaluations. The review included 11 economics evalutions,9 pertaining to IPF and 2 pertaining to PPF. Seven studies on costs and resource use in the UK are included 5 pertaining to IPF and 2 pertaining to PPF. A complete description of the review methods is provided in CS Appendix E.

The model includes the following costs: treatment acquisition costs, health state unit costs and resource use, disease monitoring costs, liver function monitoring costs, supplementary oxygen costs, adverse reaction costs and resource use, acute exacerbations cost, end of life costs and miscellaneous unit costs. In accordance with the NICE reference case and NHS perspective was taken and whenever

possible, HCRU cost inputs were sourced from the NHS Reference Costs 2024/25 and PSSRU 2024. Costs were inflated to reflect 2024 prices.

Drug acquisition costs

Nerandomilast and Nintedanib treatment dosing and hence treatment acquisition costs are the same for both IPF and PPF, with per cycle costs differing according to respective treatment discontinuation parameters for each disease included in the model. List prices were obtained from the BNF and eMIT for nintedanib and pirfenidone respectively. The company applies a lower cost for pirfenidone during the first cycle due to the dose escalation period upon initiation. The company has applied a Patient Access Scheme (PAS) discount for nerandomilast and nintedanib, reducing the acquisition costs per model cycle to [redacted] for nerandomilast and [redacted] for nintedanib respectively. The company assumes a zero drug administration costs as all treatments are administered orally. Table 26 below summarises the list price and cost per cycle for each treatment.

The EAG are satisfied with the treatment acquisition costs used by the company and their application in the model.

Table 26 List price unit costs, drug acquisition cost per cycle and discounted cost for each treatment.

Treatment	Package size	Strength (mg)	Cost per pack, list price (£)	Daily dose (mg)	Tablets per day	Drug acquisition cost per cycle (£) [A]	Discounted acquisition cost per cycle (£) [A]
NERA 18 mg	60	18	3,825	36	2	11,642	[redacted]
NDB	60	150	2,151	300	2	6,547	[redacted]
PFN first week	63	267	14.59	801	3	Cycle 1: 132	Cycle 1: 132
PFN second week	63	267	14.59	1,602	6		
PFN after 2 weeks	84	801	42.69	2,403	3	Cycle 2+: 139	Cycle 2+: 139

Key: BNF, British National Formulary; eMIT, electronic market information tool; FVC, forced vital capacity; NDB, nintedanib; NERA, nerandomilast; PFN, pirfenidone; PPF, progressive pulmonary fibrosis; SE, standard error.
Note: A dose intensity of 100% was assumed for all included treatments.
A: EAG base case

Source: NDB cost per pack extracted from BNF[41]; PFN cost per pack extracted from eMIT.[42]

Liver function monitoring costs

Liver function monitoring costs were applied in the model for patients receiving nintedanib or pirfenidone. The company explain that this is a justifiable cost as it is mandated in the use of pirfenidone and recommended by NHS guidance with nintedanib. The company do not attribute liver function test costs to nerandomilast as no one taking nerandomilast 18mg monotherapy in the FIBRONEER Trials experienced 'potentially severe' drug induced liver injury. The application of LFT costs has been used in previous technology appraisals for nintedanib and pirfenidone (TA 379, TA747, TA 504).[11, 13, 14] Previous methods have used the NHS Reference Costs for LFT; however, the company added the cost of a 10-minute nurse appointment following discussions with clinical experts. The company assumes this cost is incurred monthly for the first cycle and once per cycle (every 3 months) thereafter, for the proportion of the cohort who remain on treatment over time. In a scenario analysis the company apply the cost of a 60-minute nurse appointment as clinical feedback advised the appointment was usually longer. Nurse's salary was sourced from the Unit Costs of Health and Social Care 2024 Manual.

The EAG's clinical expert advisor felt that liver function tests might be used initially in UK clinical practice for patients receiving nerandomilast but was satisfied that this practice would reduce over time if the lack of drug induced liver injury was found to feed through in routine clinical practice. The EAG accepts the company's base case assumption.

Disease monitoring unit costs

The unit costs for each component included in the model were sourced from either the NHS Reference Costs 2024/25 or PSSRU 2024. Disease monitoring costs included the following components: Hospitalisations without ICU, ICU stay with or without mechanical ventilation, A&E visits, ambulance use, GP visits, specialist visits, nurse visits, physiotherapist visits, occupational therapy visits and 'other' visits. The company explain that

hospitalisations due to acute exacerbation were excluded from this category. The company include a separate one-off cost for acute exacerbations. The company apply a weighted average cost of all acute exacerbation patients with and without hospitalisation.

Frequency use data in the economic model for the IPF cohort was derived from the statistical analysis of FIBRONEER Trial IPF data at 52 weeks (data base lock 2). Each FVC% predicted health state is associated with a different resource use. Similarly, frequency use data in the economic model for the PPF was derived from the statistical analysis of FIBRONEER Trial ILD data at 52 weeks (data base lock 2). Unit costs and per cycle frequency for each component is used to calculate the disease monitoring costs per cycle for each FVC% predicted health state. Unit costs for each component of disease monitoring are outlined in the table below. Resource use frequencies from the INBUILD trial are also displayed in table 27 below.

Table 27 Per cycle frequencies of disease monitoring categories in the IPF population

FVC % pred	Hosp wo ICU	Hosp w ICU	A&E visits	Amb use	GP visits	Spec visits	Nurse visits	Physio visits	OT visits	Other visits
≥ 110	0.07	0.01	0.03	0.01	0.20	0.33	0.01	0.03	0.00	0.03
100–109.9	0.06	0.01	0.05	0.01	0.16	0.25	0.02	0.00	0.00	0.01
90–99.9	0.04	0.01	0.07	0.02	0.12	0.19	0.01	0.01	0.00	0.02
80–89.9	0.06	0.01	0.05	0.02	0.15	0.17	0.01	0.01	0.00	0.03
70–79.9	0.06	0.01	0.05	0.02	0.15	0.17	0.03	0.01	0.00	0.02
60–69.9	0.05	0.01	0.06	0.02	0.12	0.18	0.02	0.00	0.00	0.03
50–59.9	0.08	0.01	0.07	0.03	0.24	0.20	0.06	0.01	0.00	0.02
40–49.9	0.09	0.01	0.10	0.04	0.14	0.22	0.06	0.07	0.00	0.02
30–39.9	0.22	0.01	0.15	0.07	0.11	0.26	0.07	0.00	0.00	0.04

Key: A&E, accident and emergency; Amb, ambulance; FVC % pred, forced vital capacity percent predicted; GP, general practitioner; Hosp, hospitalisation; ICU, intensive care unit; IPF, idiopathic pulmonary fibrosis; OT, occupational therapist; Physio, physiotherapist; Spec, specialist; w, with; wo, without.

Table 28 Per cycle frequencies of disease monitoring categories in the PPF population

FVC % pred	Hosp wo ICU	Hosp w ICU	A&E visits	Amb use	GP visits	Spec visits	Nurse visits	Physio visits	OT visits	Other visits
≥ 110	0.03	0.01	0.04	0.02	0.25	0.17	0.00	0.03	0.00	0.03
100–109.9	0.11	0.01	0.08	0.07	0.24	0.21	0.00	0.01	0.00	0.03
90–99.9	0.05	0.01	0.03	0.01	0.16	0.30	0.03	0.01	0.00	0.06
80–89.9	0.07	0.01	0.06	0.01	0.13	0.23	0.02	0.00	0.00	0.04
70–79.9	0.08	0.01	0.04	0.01	0.18	0.24	0.03	0.01	0.00	0.02
60–69.9	0.08	0.01	0.07	0.02	0.16	0.24	0.01	0.01	0.00	0.03
50–59.9	0.07	0.01	0.07	0.02	0.15	0.26	0.04	0.01	0.01	0.04
40–49.9	0.13	0.01	0.09	0.04	0.12	0.30	0.05	0.01	0.01	0.02
30–39.9	0.28	0.01	0.11	0.08	0.21	0.52	0.02	0.00	0.00	0.01

Key: A&E, accident and emergency; Amb, ambulance; FVC % pred, forced vital capacity percent predicted; GP, general practitioner; Hosp, hospitalisation; ICU, intensive care unit; OT, occupational therapist; Physio, physiotherapist; PPF, progressive pulmonary fibrosis; Spec, specialist; w, with; wo, without.

Table 29 Three monthly probabilities of resource use for each FVC% Pred group for PPF patients from the INBUILD Trial

FVC % pred	Hospitalisation	A&E visits	Amb use	GP visits	Spec visits	Nurse visits	Physio visits	OT visits	Other visits
≥ 110	0.12	0.10	Not reported	0.12	0.07	0.02	0.01	0.02	0.02
100–109.9	0.05	0.04	Not reported	0.10	0.14	0.01	0.01	0.01	0.01
90–99.9	0.05	0.02	Not reported	0.16	0.25	0.03	0.01	0.02	0.02
80–89.9	0.05	0.04	Not reported	0.18	0.21	0.02	0.02	0.04	0.04
70–79.9	0.05	0.03	Not reported	0.31	0.26	0.03	0.03	0.01	0.01
60–69.9	0.09	0.05	Not reported	0.19	0.23	0.03	0.00	0.01	0.01
50–59.9	0.09	0.06	Not reported	0.17	0.18	0.02	0.00	0.02	0.02
40–49.9	0.14	0.05	Not reported	0.15	0.17	0.02	0.00	0.03	0.03

Overall resource use frequencies are similar between the INBUILD and FIBRONEER ILD trials. The reported frequencies of GP visits among patients with FVC% predicted ≥100 in the INBUILD trial appear comparably smaller to frequencies reported in the FIBRONEER ILD trial. The frequency of GP visits among the 70-79.9 FVC% predicted cohort is comparably higher in the INBUILD Trial.

The company explain that there is a lack of resource use data for patients with IPF and PPF in the UK and therefore used resource use data from the FIBRONEER trial. The company states that UK- based respiratory consultants validated the resource use data used by the company, however they did express some concerns. This is outlined in the HTA validation interview report provided by the company. One clinician explained that 1 in 10 patients with a FVC % predicted <50% are referred to see a gastroenterologist. The clinicians also expressed concerns about regional differences in local community and palliative care which would impact resource use

frequency averages. For the PPF cohort one clinician felt specialist visit frequencies were low as care often involves multiple teams. The clinician also felt that nurse visits were lower than expected as anti-fibrotic treatment is often administered and supervised by nurses.

The company's systematic literature search found 4 UK based studies that report resource use in IPF, 1 in PPF and 2 conference abstracts for both IPF and PPF. However, none of these studies report resource use per health state as defined by FVC % predicted.

Previous TA747 reports frequency of healthcare resource use for PPF patients per FVC % predicted health state and were derived from the INBUILD trial. These values are shown in the table below.

A higher proportion of patients in the INBUILD Trial are European [redacted] *versus* [redacted] *of the no AF cohort in the FIBRONEER Trial. However, only 3.5 % of the participants are British and previous subgroup analysis of the INBUILD trial failed to identify significant effects of different subgroups on the cost effectiveness results. It is worth noting that the study lacked statistical power to detect such effects. Additionally, this analysis pertains to nintedanib which has a different mechanism of action to nerandomilast, and it is currently unknown if nerandomilast yields heterogenous effects across different demographics. Given the lack of UK data on resource use for IPF and PPF patients the EAG considers the data used by the company acceptable as a base case estimate. However, scenario analyses using resource use data from the INBUILD and INPULSIS trials would be beneficial.*

Table 30 Disease monitoring unit costs

Component	Unit cost (£)	Currency code/reference table
Hospitalisations without ICU (per stay)	4,009	NHS Reference Costs 2024/25;[43] Fibrosis or Pneumoconiosis; Per Stay, NEL. Currency Code: DZ25
ICU stay with or without mechanical ventilation (per day)	1,855	NHS Reference Costs 2024/25;[43] Adult Critical Care, 0-1 Organs Supported; Per Day. Currency Codes: XC06Z; XC07Z

Component	Unit cost (£)	Currency code/reference table
A&E visits	333.75	NHS Reference Costs 2024/25;[43] ER overnight stay. Emergency Medicine, Category 1-5 investigation, Category 1-5 treatment; Per Visit. Currency code: VB01Z-VB09Z
Ambulance use	271.98	NHS Reference Costs 2024/25;[43] Ambulance codes 01 - 04
GP visits	45.00	PSSRU 2024,[44] Table 9.4.2; Unit costs for a GP: Per surgery consultation lasting 10 minutes
Specialist visits	206.85	NHS Reference Costs 2024/25;[43] Consultant Led: Respiratory Medicine Service Non-Admitted Face to Face, follow-up. Currency code: 340
Nurse visits	176.45	NHS Reference Costs 2024/25;[43] Specialist Nursing, Asthma and Respiratory Nursing/Liaison, Adult, Face to face - Community Health Services. Respiratory Service. Currency Code: N08AF
Physiotherapist visits	212.91	NHS Reference Costs 2024/25;[43] Physiotherapist, Adult, One to One - Community Health Services. Respiratory Service. Currency code: A08A1
Occupational therapy visits	249.46	NHS Reference Costs 2024/25;[43] Occupational Therapist, Adult, One to One - Community Health Services. Respiratory Service. Currency Code: A06A1
Other visits	511.00	PSSRU 2024,[44] Table 6.1; Average of Non-elective inpatient stays (short stays) and Outpatient attendances

Key: A&E, accident and emergency; GP, general practitioner; ICU, intensive care unit; NEL, non-elective long stay; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.
Source: Unit costs for the categories 'GP visits' and 'Other visits' were extracted from the PSSRU 2024 Report. All other unit costs were extracted from the NHS National Cost Collection (2024/25).

The company states that they used the unit cost for physiotherapist visits and occupational therapy visits given by NHS Reference Cost 2024/25 for 'Respiratory Services', however the figure given is for 'Appliance services. The EAG have incorporated an option in the model to apply the unit cost for physiotherapist visits and occupational therapy visits for respiratory services. The company's applied unit cost and the EAG's preferred unit cost is outlined in table 31 below.

Table 31 Company and EAG preferred unit cost for physiotherapist and occupational therapist resource use

Resource	Company Unit Cost (£)	EAG preferred Unit Cost (£)
Physiotherapist	212.91	119
Occupational Therapist	249.46	145

The frequency of use for each disease monitoring component was calculated according to FVC% predicted and derived from the FIBRONEER trial data. Some frequencies reported appear implausible. For example, those with FVC% predicted greater than 100% attend hospital (without ICU) more frequently than patients with FVC% predicted 90-99.9% and attend their GP, a specialist and physiotherapists more frequently than patients with FVC% pred of 60-99.9%.

Supplemental oxygen

Supplemental oxygen use is derived from the FIBRONEER Trial data. A unit cost of £246.89 for supplemental oxygen was obtained from the NHS reference 2024/25. A scenario analysis was conducted employing the unit cost of £527.57 which was used in TA 747. The company received clinical expert advice that patients who suffer from an acute exacerbation likely need supplemental oxygen for the remainder of their lives. Thus, the proportion of patients requiring supplemental oxygen increases after an acute exacerbation and this is reflected in the model. Per cycle costs associated with supplemental oxygen therapy included in the company base case analysis by FVC % predicted health state are summarised in Table 32 below for IPF and PPF respectively.

Table 32 Share of IPF and PPF patients on oxygen therapy before and after acute exacerbation per FVC% predicted health state and associated costs.

FVC % predicted	Share of patients on oxygen therapy IPF		Share of patients on oxygen therapy PPF		Cost per cycle of supplemental oxygen therapy (IPF)		Cost per cycle of supplemental oxygen therapy (PPF)	
	Before AcEx	After AcEx	Before AcEx	After AcEx	Before acute exacerbation (£)	After acute exacerbation (£)	Before acute exacerbation (£)	After acute exacerbation (£)
≥ 110	[redacted]	[redacted]	[redacted]	[redacted]	29.65	82.18	0.00	0.00
100–109.9	[redacted]	[redacted]	[redacted]	[redacted]	30.80	85.35	47.90	99.96
90–99.9	[redacted]	[redacted]	[redacted]	[redacted]	28.42	78.75	47.53	99.18
80–89.9	[redacted]	[redacted]	[redacted]	[redacted]	40.78	113.02	45.81	95.58
70–79.9	[redacted]	[redacted]	[redacted]	[redacted]	51.34	142.27	52.13	108.78
60–69.9	[redacted]	[redacted]	[redacted]	[redacted]	75.45	209.09	69.54	145.10
50–59.9	[redacted]	[redacted]	[redacted]	[redacted]	85.64	237.34	91.36	190.63
40–49.9	[redacted]	[redacted]	[redacted]	[redacted]	138.92	246.89	121.98	246.89
30–39.9	[redacted]	[redacted]	[redacted]	[redacted]	192.49	246.89	176.94	246.89

Key: FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.

Source for share of patients: FIBRONEER-IPF E41932-00 Evidera, PPD 20 June 2025, PPF DBL2 Statistical Analysis.
Source for cost: NHS Reference Costs 2024/25

The EAG is satisfied that the model adequately accounts for the costs of supplemental oxygen and considers the increased costs incurred following an acute exacerbation to be appropriate. The EAG notes however that the increase in costs of supplemental oxygen post-acute exacerbation is applied in one cycle only. This is likely due to the memoryless nature of the Markov cohort model. However, the EAG note that supplemental oxygen use may accumulate over time due to histories of acute exacerbations, in which case the overall supplemental oxygen costs may be underestimated in the model.

Adverse reaction costs

Grade 3+ Adverse events are included in the model. The costs associated with these AE are sourced from NHS reference costs 2024/24 and are shown in the table below. In the base case, the company applied this cost as a once off cost at initiation of treatment. This method has been applied in previous technology appraisals, namely- TA 747, TA504 and TA 864. Table 33 below reports the company base case unit costs and sources for adverse events.

Table 33 Unit costs for adverse events

Adverse event	Unit cost (monthly, £)	Source	Notes
Cardiac events	2,652	NHS Reference Costs 2024/25	Cardiac Arrest; Per Stay; Weighted average of NES and NEL. Currency code: EB05
Pneumonia	8,102		Lobar, Atypical or Viral Pneumonia, with Multiple Interventions; Per Stay, Weighted average of NES and NEL. Currency Code: DZ11K-M
Diarrhoea	6,168		Gastrointestinal Infections with Single Intervention. Currency code FD01C-D
GI disorders (without diarrhoea)	6,415		Gastrointestinal Infections with Single Intervention. Currency code FD01C-D
Photosensitivity reaction	6,415		Skin Disorders with Interventions. Currency code: JD07A-C
Key: GI, gastrointestinal; NEL, non-elective long stay; NES, non-elective short stay; NHS, National Health Service.			

The EAG noted a minor error in the company submission and excel model where unit cost for photosensitivity reaction is used for GI disorders (without diarrhoea). The same currency codes are referenced as data source for unit cost of diarrhoea and unit cost of GI disorders (without diarrhoea). Thus, the unit cost for GI (without diarrhoea) should be £6,168 instead of £6,415. An option to change the unit cost of GI disorders (without diarrhoea) to £6,168 has been added to the model.

In TA 747 an adverse reaction cost of £39- equivalent to the cost of a GP visit was assumed as they found adverse reactions were mostly mild or moderate nature and had assumed all adverse reactions could be managed in primary care. However, given that only adverse reactions of grade 3 + are included in the model, the severity of such events is likely to require management in secondary care and have greater financial implications. The EAG feels that the approach used in this company submission better reflects the costs associated with adverse events.

Acute Exacerbation costs

The company apply a one- off cost of £1,641 to the proportion experiencing an acute exacerbation in each model cycle. Unit costs are sourced from NHS Reference Costs 2024/25. The risks of acute exacerbation are provided in section 3.3.4 of company submission.

The EAG are satisfied with the costing approach for acute exacerbations used in the company base case model.

End of life costs

The company applied a one-off end of life cost using data from PSSRU 2024. In a scenario analysis end of life costs were obtained from TA 1108 which used costs based on the distribution of patient deaths across home, hospital, and hospice care settings.[45]

The EAG are satisfied that the modelled end of life cost is appropriate.

5 Cost-effectiveness results

Section 5.1 summarises the company's cost-effectiveness results and section 5.2 details the EAG's additional work and preferred assumptions.

The EAG note and agree with the company assessment that severity weighting is not relevant for this assessment. Therefore, all ICERs are reported without any QALY weightings applied.

5.1 Company's cost-effectiveness results

The company preferred cost-effectiveness analyses (including base case, scenario and sensitivity analyses) are presented first for IPF (Section 5.1.1) and then for PPF (Section 5.1.2).

5.1.1 Company's base case, sensitivity and scenario analyses - IPF

Table 34 details the company's preferred base case deterministic and probabilistic analyses for IPF. Results are presented first as pairwise comparisons for Nerandomilast vs. each comparator, and a fully incremental analysis is also reported (Table 35). Given the recent increase in the range of threshold values that NICE might consider for cost-effectiveness from £20,000- £30,000 to £25,000 - £35,000, the EAG has updated the net health benefit for the company's analyses to reflect the new threshold range. Figures 12 and 13 show the probabilistic results on the cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs) respectively.

Table 34 Company's deterministic and probabilistic base-case pairwise cost-effectiveness results for IPF.

Treatment	Deterministic							Probabilistic				
	Total costs	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £25,000	NHB at £35,000	Total costs	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
NERA	[redacted]	4.54	-	-	-			[redacted]	4.51	-	-	-
BSC	12,609	3.40	[redacted]	1.14	[redacted]	[redacted]	[redacted]	12,924	3.44	[redacted]	1.06	[redacted]
NDB	[redacted]	3.61	[redacted]	0.93	[redacted]	[redacted]	[redacted]	[redacted]	3.56	[redacted]	0.95	[redacted]
PFN	13,625	3.61	[redacted]	0.93	[redacted]	[redacted]	[redacted]	13,629	3.56	[redacted]	0.95	[redacted]

Abbreviations: NERA: nerandomilast; BSC: best supportive care; ICER: incremental cost effectiveness ratio; Incr: incremental; NDB: nintedanib; NHB: net health benefit; PFN: pirfenidone; QALY: quality-adjusted life year.

Table 35 Company's deterministic and probabilistic fully incremental analysis - IPF

Treatment	Deterministic fully incremental analysis					Probabilistic fully incremental analysis		
	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £25,000	NHB at £35,000	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	-	-	-	-	-	-	-	-
PFN	[redacted]	0.21	[redacted]	[redacted]	[redacted]	[redacted]	0.12	[redacted]
NDB	-	-	[redacted]	-	-	-	-	[redacted]
NERA	[redacted]	0.93	[redacted]	[redacted]	[redacted]	[redacted]	0.95	[redacted]

Abbreviations: BSC: best supportive care; ICER: incremental cost effectiveness ratio; NDB: nintedanib; NERA: nerandomilast; NHB: net health benefit



Abbreviations: BSC, best supportive care; NDB, nintedanib; PFN: pirfenidone; PSA, probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP, willingness to pay

Figure 12 Cost-effectiveness scatter plot for IPF (Reproduced from figure 48 in company submission)



Figure 13 Cost-effectiveness acceptability curve – PAS prices; IPF (Reproduced from figure 49 in company submission)

Company's sensitivity and scenario analyses - IPF

Deterministic Sensitivity analysis: IPF

The company performed deterministic one-way sensitivity analysis (OWSA), to investigate the impact of varying each model parameter at the lower and upper bound values of the 95% confidence interval. The results of the 10 most impactful parameter changes are shown for each pairwise comparison with nerandomilast in Figures 53-55 of the company submission. Treatment based mortality parameters for nerandomilast, and treatment waning switch (TTD Efficacy Switch Time Point) were the two most impactful parameters in all three pairwise deterministic analysis. The mortality hazard ratio between nerandomilast and nintedanib was the most impactful parameter in the deterministic analysis of nerandomilast versus nintedanib.

Scenario analyses

Company provided scenario analyses in the original company submission and in response to clarification queries are summarised in Table 36 below.

Table 36 Company provided deterministic scenario analyses for IPF – applied to company preferred base case (reproduced from Table 91 of the company submission and company response to clarification queries)

Scenario	Category	Base case value	Scenario value	Company Rationale	ICER vs BSC (£/QALY)	ICER vs NDB (£/QALY)	ICER vs PFN (£/QALY)
-	Base case				[redacted]	[redacted]	[redacted]
1	NDB treatment effect source (all efficacy endpoints)	IPD meta-regression*	Using INPULSIS data	Explore a wide range of potential treatment effect sources given that nintedanib was not a direct comparator in the trial	[redacted]	[redacted]	[redacted]
2	Health state transitions	Equal to NERA	NDB = IPD meta-regression	Estimate the impact of health state transitions differing between treatments	[redacted]	[redacted]	[redacted]
3			PFN = NMA		[redacted]	[redacted]	[redacted]
4			NDB = IPD meta-regression; PFN = NMA		[redacted]	[redacted]	[redacted]
5		Not dependent on AcEx	Increased risk following AcEx		[redacted]	[redacted]	[redacted]
6	Mortality	Gamma	Weibull	Exploring alternative models that were noted as plausible by clinicians for robustness	[redacted]	[redacted]	[redacted]
7			Log-logistic		[redacted]	[redacted]	[redacted]

Scenario	Category	Base case value	Scenario value	Company Rationale	ICER vs BSC (£/QALY)	ICER vs NDB (£/QALY)	ICER vs PFN (£/QALY)
8		FIBRONEER trial data for NERA	NERA ITC results	Using more mature data for nerandomilast	[redacted]	[redacted]	[redacted]
9	AcEx	Vary by treatment	Equal to NERA for all treatments	Based on clinical validation	[redacted]	[redacted]	[redacted]
10		Constant	Vary by health state		[redacted]	[redacted]	[redacted]
11	TTD	Stopping rule for all treatments	Stopping rule for NERA only	Impact of formal stopping rule for nerandomilast and comparators	[redacted]	[redacted]	[redacted]
12		Waning of [redacted] cycles	Waning of [redacted] cycles	Alignment with FIBRONEER-IPF follow-up	[redacted]	[redacted]	[redacted]
13		Constant discontinuation rate	Parametric-based discontinuation rate	Clinical validation, discontinuation rate may not be constant	[redacted]	[redacted]	[redacted]
14	Health state utilities	Pooled FIBRONEER-IPF and INPULSIS	Literature (Rinciog 2017)[46]	Impact of using previously accepted utility values in NICE TA747.[46, 47]	[redacted]	[redacted]	[redacted]
15	Disutility of acute exacerbation	Pooled FIBRONEER-IPF and INPULSIS	INPULSIS	Based on clinical validation: pooled trial-based utilities after acute exacerbation higher than clinicians expected	[redacted]	[redacted]	[redacted]

Scenario	Category	Base case value	Scenario value	Company Rationale	ICER vs BSC (£/QALY)	ICER vs NDB (£/QALY)	ICER vs PFN (£/QALY)
16	Costs	SupOx costs: NHS Ref 24/25	SupOx costs: Rinciog 2017	Alignment with earlier TAs in this area	[redacted]	[redacted]	[redacted]
17		EoL costs: PSSRU	EoL costs: TA1108	Exploring the impact of using a greater cost of EoL	[redacted]	[redacted]	[redacted]
18		Nurse time LFM: 10 min	Nurse time LFM: 60 min	Clinical feedback notes that 10 minutes too short	[redacted]	[redacted]	[redacted]
19	Additional scenario analyses in response to clarification queries	Treatment waning	50 years	Exploring uncertainty around continued treatment benefit following treatment discontinuation	[redacted]	[redacted]	[redacted]
			5 years		[redacted]	[redacted]	[redacted]
20		Health state utility	FIBRONEER-IPF Trial HSUV only	Exploring impact of using FIBRONEER trial data only	[redacted]	[redacted]	[redacted]
21		LFT disutility	No LFT disutility	Potential for double counting as likely captured by HSUV	[redacted]	[redacted]	[redacted]

Key: AcEx, acute exacerbation; EoL, end of life; FVC, forced vital capacity; ICER, incremental cost-effectiveness ratio; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; ITC, indirect treatment comparison; LFM, liver function monitoring; NDB, nintedanib; NERA, nerandomilast; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PFN, pirfenidone; PSSRU, Personal Social Services Research Unit; SupOx, supplemental oxygen; TA, technology appraisal; TTD, time to treatment discontinuation.
Notes: *for change in FVC over time the base case value for nintedanib is equal to nerandomilast.

5.1.2 Company's base case, sensitivity and scenario analyses - PPF

Table 37 details the company's preferred base case deterministic and probabilistic analyses for IPF. Results are presented first as pairwise comparisons for Nerandomilast vs. each comparator, and a fully incremental analysis is also reported (Table 38). The results reported reflect those provided in the company submitted addendum to the submission correcting a parameter input error for the mortality HR used in the model. Figures 14 and 15 illustrate the probabilistic results on the scatter plot of the cost-effectiveness plane and CEACs respectively.

Table 37 Company's deterministic and probabilistic base-case cost-effectiveness results for PPF.

	Deterministic Analysis							Probabilistic Analysis				
	Total costs	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £25,000	NHB at £35,000	Total costs	Total QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
Nerandomilast	[redacted]	4.12	-	-	-		-	[redacted]	4.09	-	-	-
BSC	17,458	3.32	[redacted]	0.8	[redacted]	[redacted]	[redacted]	17,697	3.32	[redacted]	0.76	[redacted]
Nintedanib	[redacted]	3.65	[redacted]	0.47	[redacted]	[redacted]	[redacted]	[redacted]	3.62	[redacted]	0.47	[redacted]

Abbreviations: BSC: best supportive care; QALY: quality-adjusted life year; ICER: incremental cost effectiveness ratio; NHB: net health benefit.

Table 38 Company's deterministic fully incremental analysis- PPF

Treatment	Deterministic			Probabilistic		
	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	-	-	-	-	-	-
Nintedanib	-	-	[redacted]	[redacted]	0.3	[redacted]
Nerandomilast	[redacted]	0.80	[redacted]	[redacted]	0.77	[redacted]

Abbreviations: NERA: nerandomilast; BSC: best supportive care; NDB: nintedanib; QALY: quality-adjusted life year ICER: incremental cost effectiveness ratio



Figure 14 Company base case, cost-effectiveness scatter plot for PPF at a WTP Threshold of £35,000



Figure 15 Company preferred base case cost-effectiveness acceptability curves for PPF

Deterministic Sensitivity analysis: PPF

The company performed deterministic one-way sensitivity analysis (OWSA), to investigate the impact of varying each model parameter at the lower and upper bound values of the 95% confidence interval. The results of the 10 most impactful parameter changes are shown for each pairwise comparison with nerandomilast in the tornado diagrams in Figures 56 and 57 of the company submission addendum. Treatment-based mortality parameters for nerandomilast, treatment waning switch, and discontinuation probability per cycle are the most impactful for each comparator.

Scenario analysis

Company provided scenario analyses in the original company submission and in response to clarification queries are summarised in Table 39 below.

The EAG noted the following discrepancies between ICER values reported in the company submission addendum (Table 92) and the updated model for PPF:

- *Base case ICER value reported in company's addendum for nerandomilast vs. nintedanib reported as [redacted], ICER value from company addendum model (aligned with Table 82 base case of the addendum document and the base case updated PPF model): [redacted].*

- *ICER value reported in company's addendum between nerandomilast and nintedanib when acute exacerbation varies by health state is [redacted]. ICER value from the updated model for PPF is [redacted],*

- *ICER value reported in company's addendum between nerandomilast and nintedanib when acute exacerbation risk is equal to that of nerandomilast is [redacted], ICER value from the updated model for PPF is [redacted]*

Where there are discrepancies between the submitted economic model file and the addendum report, the EAG considers the economic model results to be correct and

has reported the corrected values in the table below, pending company confirmation. In all cases the discrepancies in reported ICER are relatively minor.

Table 39 Company provided deterministic scenario analyses for PPF – applied to company preferred base case (reproduced from Table 92 of the company submission addendum and clarification responses addendum).

Scenario	Category	Base case value	Scenario value	Rationale	ICER vs BSC (£/QALY)	ICER vs NDB (£/QALY)[A]
-	Base case				[redacted]	[redacted]
1	NDB treatment effect source (all efficacy endpoints)	IPD meta-regression*	Using INBUILD data	Explore a wide range of potential treatment effect sources given that nintedanib was not a direct comparator in the trial	[redacted]	[redacted]
2	Health state transitions	Equal to NERA	NDB = IPD meta-regression	Estimate the impact of health state transitions differing between treatments	[redacted]	[redacted]
3		Not dependent on AcEx	Increased risk following AcEx		[redacted]	[redacted]
4	Mortality	Gamma	Weibull	Exploring alternative models that were noted as plausible by clinicians for robustness	[redacted]	[redacted]
5			Log-normal		[redacted]	[redacted]
6		FIBRONEER trial data for NERA	NERA ITC results	Using more mature data for nerandomilast	[redacted]	[redacted]
7	AcEx	Vary by treatment	Equal to NERA for all treatments [B]	Based on clinical validation	[redacted]	[redacted]
8		Constant	Vary by health state		[redacted]	[redacted]
9	TTD	Stopping rule for all treatments	Stopping rule for NERA only	Impact of formal stopping rule for nerandomilast and comparators	[redacted]	[redacted]
10		Waning of [redacted] cycles	Waning of [redacted] cycles	Alignment with FIBRONEER-ILD follow-up	[redacted]	[redacted]
11		Constant discontinuation rate	Parametric-based discontinuation rate	Clinical validation, discontinuation rate may not be constant	[redacted]	[redacted]

Scenario	Category	Base case value	Scenario value	Rationale	ICER vs BSC (£/QALY)	ICER vs NDB (£/QALY)[A]
12	Health state utilities	Pooled FIBRONEER-ILD and INBUILD	Literature (TA747)[46]	Impact of using previously accepted utility values in NICE TA747.[46, 47]	[redacted]	[redacted]
13	Disutility of acute exacerbation	Pooled FIBRONEER-ILD and INBUILD	INBUILD	Based on clinical validation: pooled trial-based utilities after acute exacerbation higher than clinicians expected	[redacted]	[redacted]
14	Costs	SupOx costs: NHS Ref 24/25	SupOx costs: Rinciog 2017	Alignment with earlier TAs in this area	[redacted]	[redacted]
15		EoL costs: PSSRU	EoL costs: TA1108	Exploring the impact of using a greater cost of EoL	[redacted]	[redacted]
16		Nurse time LFM: 10 min	Nurse time LFM: 60 min	Clinical feedback notes that 10 minutes too short	[redacted]	[redacted]
17	Additional scenarios in response to clarification queries	Treatment effect waning	50 years	Exploring uncertainty around continued treatment benefit following treatment discontinuation	[redacted]	[redacted]
			5 years		[redacted]	[redacted]
18		HSUV based on FIBRONEER Trial only	FIBRONEER-ILD Trial data for HSUV	Exploring impact of using FIBRONEER Trial data only	[redacted]	[redacted]
19		LFT disutility	No LFT disutility applied	Potential for double counting as likely captured by HSUV	[redacted]	[redacted]

Key: AcEx, acute exacerbation; EoL, end of life; FVC, forced vital capacity; ICER, incremental cost-effectiveness ratio; IPD, individual patient-level data; IPF, idiopathic pulmonary fibrosis; ITC, indirect treatment comparison; LFM, liver function monitoring; NDB, nintedanib; NERA, nerandomilast; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PFN, pirfenidone; PSSRU, Personal Social Services Research Unit; SupOx, supplemental oxygen; TA, technology appraisal; TTD, time to treatment discontinuation. **Notes:** *for change in FVC over time the base case value for nintedanib is equal to nerandomilast; [A] Where there are discrepancies between the submitted economic model file and the addendum report, the EAG considers the economic model results to be correct and has reported the corrected values in the table, pending company confirmation. [B] For Nera vs. NDB, ICER not directly reproducible in the company's economic model due to non-functional switch. Company manually recalculated at Factual Accuracy Check stage, but EAG would appreciate access to a model with all switches fully functional to enable replication of results.

5.2 EAG's additional analyses

5.2.1 Model validation and face validity check

The company described a range of model face validity checks. The model structure, key model inputs and assumptions were validated by UK clinical experts who verified that the nature of the disease and that the treatment pathway reflects what is seen clinically and how the disease is treated in UK NHS practice. A senior modeller who was not involved in this model's construction but worked within the developer's organisation independently reviewed the model. The company performed internal validation by varying input parameters and assumptions in the model to assess impact on model outputs. A health economist validated the model's methodology and credibility using the TECH- VER check list.[48] Furthermore, the company conducted a probabilistic sensitivity analysis and a series of one way and scenario analyses to assess the robustness of the model.

During the appraisal process, the company identified a model input error regarding the mortality HR obtained from the NMR for the comparison of nerandomilast vs. nintedanib used in the PPF population. The company subsequently submitted an addendum to their report with corrected parameter inputs. The EAG has used these updated parameter inputs in the economic model and updated results throughout the report. The EAG have some concerns regarding the updated parameters (described as footnotes to the relevant tables throughout the report).

The EAG used the CADTH model validation tool to evaluate the company's post clarification model. It was not possible to re-validate using the company addendum model due to time constraints. The model satisfies most of the 53 items outlined in the CADTH checklist. The EAG has made several observations during the checking process, and these are summarised in Table 40 below. The EAG does not necessarily consider these points to be modelling errors but has provided commentary where further information would have been helpful to more fully assess the cost-effectiveness case.

Table 40 Quality assessment checklist – EAG summary comments

Item number	Description	EAG comment on non-compliance
2	Model examines key subgroups	Subgroup analysis based on disease severity (as defined by FVC% predicted) not possible
21	Distinguishes data that are based on extrapolation methods	The model file does not include raw Kaplan Meier curves for outcomes included in the model as survival analyses. This somewhat limits the EAG's ability to validate estimates, but it is noted that the KM curves are available within the company submission documentation. The EAG would have preferred an opportunity to explore a full range of survival curves, including independently fitted curves.
28	Macros are exclusively related to first- or second-order simulation and model navigation	No, Macros are used to replicate the model engine for each intervention and comparator. This renders it difficult to fully inspect the different traces in a single file, but the EAG notes it is possible to run each treatment arm independently to inspect the results.
47	You can work backward from the results of the model to input entry.	No. Results can be traced back to 'results pasted by Macro' sheet only
48	You can work forward from input entry to the results of a single Monte Carlo simulation.	No. The outputs from Monte Carlo simulation cannot be traced back to inputs because the model does not use spreadsheet formulas to calculate result outputs, instead this calculation is done using a VBA macro limiting the traceability of results.
49	Avoidance of problematic Excel functions	CHOOSE and INDEX are used frequently throughout the model. Although the EAG is satisfied that this has not impacted the validity of the model.
50	No hidden sheets/rows/columns	The model does contain hidden rows and columns. When these hidden cells are revealed, they are empty.
51	No user-created formulas embedded in VBA	The model does contain user created formulas embedded in VBA

5.2.2 EAG's exploratory and preferred analyses (IPF)

Additional scenario analyses conducted by the EAG are described in Table 41 below.

Table 41 Summary of EAG conducted scenario analyses IPF

Scenario No.	Company's base-case	EAG scenario	Justification for EAG assumption	Section EAG report
1	Assume transition probabilities equal to nerandomilast 18mg for all active AF treatments	Apply comparative data across treatments from the ITC (NMR)	Makes best use of the available evidence and avoids need for unnecessary assumptions. Facilitates inclusion of uncertainty in the PSA	4.2.5
2	Assumes Nintedanib and PFN health state transition probabilities are equal for IPF	Apply comparative data from the Bayesian NMA	Avoids unnecessary assumptions of equivalence and facilitates inclusion of uncertainty in the PSA	4.2.5
3	PFN mortality assumed equal to nintedanib for IPF	Apply mortality HR from the Bayesian NMA	Avoids unnecessary assumptions of equivalence and facilitates inclusion of uncertainty in the PSA	4.2.5
4	PFN acute exacerbations assumed equal to nintedanib for IPF	Apply OR of 52-week acute exacerbations from the Bayesian NMA	Avoids unnecessary assumptions of equivalence and facilitates inclusion of uncertainty in the PSA	4.2.5
5	Apply a constant rate of discontinuation for nintedanib from INPULSIS / INBUILD studies for IPF / PPF	Apply HR of time to treatment discontinuation from NMR	Makes best use of all the available IPD data and maintains consistency with EAG preferred approach of using the NMR where possible for comparisons vs. nintedanib.	4.2.5
6	Assumes PFN treatment discontinuation = nintedanib	Apply OR from NMA	Avoids unnecessary assumptions of equivalence and	4.2.5

Scenario No.	Company's base-case	EAG scenario	Justification for EAG assumption	Section EAG report
			facilitates inclusion of uncertainty in the PSA	
7	Apply treatment waning assumption for [redacted] post initiation for the proportion discontinued from treatment for IPF and PPF respectively across all active treatment comparators	Remove company's treatment waning approach	Company's approach does not adequately capture the impact of treatment waning which is more likely to occur shortly after discontinuation.	4.2.5
8	Acute exacerbation disutilities applied over 10 days	Applied over 30 days	EAG correction to apply full disutility from the company's regression models in the model engine.	4.2.6
9	Include liver function test disutility	Remove disutility	EAG are concerned that the source data are not generalisable to PF, or to liver function tests.	4.2.6
10	AE costs and utilities include some minor discrepancies from source	Discrepancies addressed	Minor adjustment to ensure accuracy of parameter inputs.	4.2.6 & 4.2.7
11	Physiotherapist cost = £212.91. Occupational therapist cost = £249.41	Physiotherapist cost = £119. Occupational therapist cost = £145	Applying physiotherapist / OT unit cost associated with respiratory services, as opposed to appliance services	4.2.7
EAG BC	Scenarios 1-11 combined (IPF); Scenarios 1,3,5,7-11 combined (PPF)			
Add. Sc A	HR parameter inputs – as per company model (IPF)	HR input as per company addendum (IPF)	Scenario exploring the impact of alternative HR input, pending company confirmation of correct data input for IPF	N/A
Add Sc B, C, D, E	EAG base case	Apply treatment effectiveness	All analyses from same methodological approach.	4.2.5

Scenario No.	Company's base-case	EAG scenario	Justification for EAG assumption	Section EAG report
		parameters form Bayesian NMA		
Add Sc F, G, H, I	EAG base case	Setting HRs =1 for treatment effectiveness parameters where non-significant differences between active treatment arms	Successive scenarios gradually reducing modelled treatment benefit, moving towards an alternative cost-comparison consideration	4.2.5 & 5.2

Results of the EAG preferred assumptions are detailed in Table 42, with additional scenario analyses applied to the EAG preferred base case illustrated in Table 43. Figures 16 and 17 illustrate the EAG preferred base case probabilistic results on the scatter plot of the cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs) respectively.

In all cases, the company and EAG are aligned in preferring not to apply a severity modifier for this assessment. All ICERs are therefore presented assuming a severity modifier of 1.0 (i.e., no QALY weighting applied).

Table 42 Impact of EAG preferred assumptions on the ICER (IPF)

Comparator	Total costs	Total Lys	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
Company base case analysis						
NERA 18 mg	[redacted]	5.96	4.54			
BSC	[redacted]	4.46	3.40	[redacted]	1.14	[redacted]
NDB	[redacted]	4.74	3.61	[redacted]	0.93	[redacted]
PFN	[redacted]	4.74	3.61	[redacted]	0.93	[redacted]
Scenario 1 – Apply rate ratio from NMR for NDB health state transition probabilities (Rate ratio: Nera 18mg vs. NDB: [redacted])						
NERA 18 mg	[redacted]	5.96	4.54			
BSC	[redacted]	4.46	3.40	[redacted]	1.14	[redacted]
NDB	[redacted]	4.74	3.61	[redacted]	0.92	[redacted]
PFN	[redacted]	4.74	3.61	[redacted]	0.93	[redacted]
Scenario 2 – As per scenario 1, plus apply OR from NMA for PFN health state transition probabilities (Odds ratio: Nera 18mg vs. PFN: [redacted]) [A]						
NERA 18 mg	[redacted]	5.96	4.54			
BSC	[redacted]	4.46	3.40	[redacted]	1.14	[redacted]
NDB	[redacted]	4.74	3.61	[redacted]	0.92	[redacted]
PFN	[redacted]	4.75	3.62	[redacted]	0.92	[redacted]

Comparator	Total costs	Total Lys	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
Scenario 3 – Apply HR of mortality from NMA; Nerandomilast vs. Pirfenidone ([redacted])						
NERA 18 mg	[redacted]	5.96	4.54			
BSC	[redacted]	4.46	3.40	[redacted]	1.14	[redacted]
NDB	[redacted]	4.74	3.61	[redacted]	0.93	[redacted]
PFN	[redacted]	4.99	3.80	[redacted]	0.74	[redacted]
Scenario 4 – Apply OR from NMA for calculating risk of acute exacerbations per cycle: Nerandomilast 18mg vs. PFN ([redacted])						
NERA 18 mg	[redacted]	5.96	4.54			
BSC	[redacted]	4.46	3.40	[redacted]	1.14	[redacted]
NDB	[redacted]	4.74	3.61	[redacted]	0.93	[redacted]
PFN	[redacted]	4.74	3.61	[redacted]	0.93	[redacted]
Scenario 5 – Apply Treatment discontinuation HR from NMR for nerandomilast 18mg vs. NDB (0.31) [B]						
NERA 18 mg	[redacted]	5.96	4.54			
BSC	[redacted]	4.46	3.40	[redacted]	1.14	[redacted]
NDB	[redacted]	4.74	3.60	[redacted]	0.93	[redacted]
PFN	[redacted]	4.74	3.60	[redacted]	0.93	[redacted]
Scenario 6 – As per scenario 5 + Apply Treatment discontinuation OR from NMA for nerandomilast 18mg vs. PFN ([redacted]) [B]						
NERA 18 mg	[redacted]	5.96	4.54			

Comparator	Total costs	Total Lys	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
BSC	[redacted]	4.46	3.40	[redacted]	1.14	[redacted]
NDB	[redacted]	4.74	3.60	[redacted]	0.93	[redacted]
PFN	[redacted]	4.74	3.61	[redacted]	0.93	[redacted]
Scenario 7 – remove company's continued treatment benefit post discontinuation assumption						
NERA 18 mg	[redacted]	5.59	4.25			
BSC	[redacted]	4.46	3.40	[redacted]	0.86	[redacted]
NDB	[redacted]	4.63	3.52	[redacted]	0.73	[redacted]
PFN	[redacted]	4.63	3.52	[redacted]	0.73	[redacted]
Scenario 8 – Apply EAG correction to application of acute exacerbation disutilities						
NERA 18 mg	[redacted]	5.96	4.53			
BSC	[redacted]	4.46	3.39	[redacted]	1.14	[redacted]
NDB	[redacted]	4.74	3.60	[redacted]	0.93	[redacted]
PFN	[redacted]	4.74	3.60	[redacted]	0.93	[redacted]
Scenario 9 (remove liver function test disutility)						
NERA 18 mg	[redacted]	5.96	4.54			
BSC	[redacted]	4.46	3.40	[redacted]	1.14	[redacted]
NDB	[redacted]	4.74	3.62	[redacted]	0.92	[redacted]
PFN	[redacted]	4.74	3.62	[redacted]	0.92	[redacted]

Comparator	Total costs	Total Lys	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
Scenario 10 - Apply EAG preferred AE assumptions (include GI perforation, rescale utility values and apply corrected NHS reference costs)						
NERA 18 mg	[redacted]	5.96	4.54			
BSC	[redacted]	4.46	3.40	[redacted]	1.14	[redacted]
NDB	[redacted]	4.74	3.61	[redacted]	0.93	[redacted]
PFN	[redacted]	4.74	3.61	[redacted]	0.93	[redacted]
Scenario 11 – Apply corrected NHS reference costs for Physiotherapy and Occupational Therapy visits						
NERA 18 mg	[redacted]	5.96	4.54			
BSC	[redacted]	4.46	3.40	[redacted]	1.14	[redacted]
NDB	[redacted]	4.74	3.61	[redacted]	0.93	[redacted]
PFN	[redacted]	4.74	3.61	[redacted]	0.93	[redacted]
EAG preferred base case analysis - deterministic (Scenarios 1-11 combined)						
NERA 18 mg	[redacted]	5.59	4.25			
BSC	[redacted]	4.46	3.39	[redacted]	0.86	[redacted]
NDB	[redacted]	4.63	3.53	[redacted]	0.72	[redacted]
PFN	[redacted]	4.81	3.67	[redacted]	0.57	[redacted]
EAG preferred base case analysis - probabilistic						
NERA 18 mg	[redacted]	5.61	4.25			
BSC	[redacted]	4.53	3.44	[redacted]	0.82	[redacted]

Comparator	Total costs	Total Lys	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
NDB	[redacted]	4.64	3.53	[redacted]	0.73	[redacted]
PFN	[redacted]	4.86	3.71	[redacted]	0.55	[redacted]

[A] Note, this scenario analysis applies the EAG corrected value for the OR from the NMA for health state progression for Nerandomilast 18mg vs. PFN as opposed to Nerandomilast 9mg vs. PFN.

[B] The EAG note that the company's submitted addendum changed the HR, but the EAG were unable to trace the updated number in the statistical NMR report. The EAG therefore retain the HR value from the NMR report pending company confirmation of the correct HR value.



Figure 16 Incremental cost-effectiveness plane for EAG base case (IPF)



Figure 17 Cost-effectiveness acceptability curve for EAG base case (IPF)

Table 43 Additional scenario analyses undertaken by the EAG, applied to the EAG preferred base case (IPF)

Comparator	Total costs	Total Lys	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
EAG preferred base case analysis						
NERA 18 mg	[redacted]	5.59	4.25			
BSC	[redacted]	4.46	3.39	[redacted]	0.86	[redacted]
NDB	[redacted]	4.63	3.53	[redacted]	0.72	[redacted]
PFN	[redacted]	4.81	3.67	[redacted]	0.57	[redacted]
Additional Scenario A – Apply company updated treatment discontinuation HRs for IPF (Nera 18mg vs. NDB), as per company addendum [A]						
NERA 18 mg	[redacted]	5.59	4.25			
BSC	[redacted]	4.46	3.39	[redacted]	0.86	[redacted]
NDB	[redacted]	4.66	3.56	[redacted]	0.69	[redacted]
PFN	[redacted]	4.81	3.67	[redacted]	0.57	[redacted]
Scenarios prioritising NMA clinical effectiveness inputs						
Additional Scenario B – Apply OR from NMA for all health state transition probabilities (Nera 18mg vs. NDB: [redacted]; Nera 18mg vs. PFN: [redacted]; Nera 18mg vs. BSC: [redacted]						
NERA 18 mg	[redacted]	5.60	4.26	[redacted]		[redacted]
BSC	[redacted]	4.46	3.39	[redacted]	0.86	[redacted]
NDB	[redacted]	4.62	3.52	[redacted]	0.73	[redacted]
PFN	[redacted]	4.81	3.67	[redacted]	0.58	[redacted]
Additional Scenario C – Apply HR of mortality from NMA for all comparisons: Nerandomilast vs. Pirfenidone ([redacted]); Nerandomilast vs. NDB ([redacted]); Nerandomilast vs. BSC ([redacted])						
NERA 18 mg	[redacted]	5.56	4.23			
BSC	[redacted]	4.46	3.39	[redacted]	0.84	[redacted]
NDB	[redacted]	4.71	3.59	[redacted]	0.64	[redacted]
PFN	[redacted]	4.75	3.62	[redacted]	0.61	[redacted]

Comparator	Total costs	Total Lys	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
Additional Scenario D – Apply OR of treatment discontinuation at 52 weeks from NMA for all comparisons: Nerandomilast vs. Pirfenidone ([redacted]); Nerandomilast vs. NDB ([redacted]).						
NERA 18 mg	[redacted]	5.59	4.25			
BSC	[redacted]	4.46	3.39	[redacted]	0.86	[redacted]
NDB	[redacted]	4.63	3.53	[redacted]	0.72	[redacted]
PFN	[redacted]	4.81	3.67	[redacted]	0.57	[redacted]
Additional Scenario E – Scenarios A+B+C combined – priority given to NMA for all treatment effect sizes in the model.						
NERA 18 mg	[redacted]	5.57	4.24			
BSC	[redacted]	4.46	3.39	[redacted]	0.85	[redacted]
NDB	[redacted]	4.71	3.59	[redacted]	0.65	[redacted]
PFN	[redacted]	4.75	3.62	[redacted]	0.61	[redacted]
Scenarios assuming equivalence of clinical outcomes across active treatment arms (Applied to EAG base case)						
Additional Scenario F – Assume all active treatments are equivalent on all outcomes except mortality and treatment discontinuation						
NERA 18 mg	[redacted]	5.59	4.25			
BSC	[redacted]	4.46	3.39	[redacted]	0.86	[redacted]
NDB	[redacted]	4.62	3.52	[redacted]	0.73	[redacted]
PFN	[redacted]	4.78	3.64	[redacted]	0.61	[redacted]
Additional Scenario G – Assume equivalence of all active treatments for transition probabilities, acute exacerbation and mortality (equal to BSC); allow differences in time to treatment discontinuation [B]						
NERA 18 mg	[redacted]	4.46	3.39			
NDB	[redacted]	4.46	3.39	[redacted]	-	-

Comparator	Total costs	Total Lys	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
PFN	[redacted]	4.46	3.39	[redacted]	-	-
Additional Scenario H – Assume equivalence of all active treatments for transition probabilities, acute exacerbation and mortality (equal to BSC); all treatment discontinuation curves = nerandomilast [C]						
NERA 18 mg	[redacted]	4.46	3.39			
NDB	[redacted]	4.46	3.39	[redacted]	-	-
PFN	[redacted]	4.46	3.39	[redacted]	-	-
Additional Scenario I – Assume equivalence of all active treatments for transition probabilities, acute exacerbation and mortality and assume 1 year of treatment for all active comparators, no treatment discontinuation [C]						
NERA 18 mg	[redacted]	0.96	0.90			
NDB	[redacted]	0.96	0.90	[redacted]	-	-
PFN	[redacted]	0.96	0.90	[redacted]	-	-

[A] Applies company updated HRs as per company addendum. Not included in EAG base case due to discrepancies between addendum and original statistical analysis report, pending company confirmation.

[B] Achieved by setting all HRs in the model for FVC % predicted decline, acute exacerbation and mortality equal to 1 for NERA 18mg vs BSC using the NMA (i.e. all life year gains set equal to BSC). Risk of mortality HR for NDB vs NERA 18 mg also set to 1. NDB and PFN assumed equivalent to NERA 18 mg using the switches in the model for FVC % predicted decline and acute exacerbation. Switch must be also set to "Yes" for NERA 18 mg to use ITC results in each outcome. Essentially provides the results of a cost-comparison analysis amongst the active treatments.

[C] Implementation notes: Adaptations to 'clinical inputs' sheet, applied to EAG preferred base case model configuration.
Scenario C: Cell M26: No→Yes; M27: No→Yes; M65: No→Yes; M77:T80 (set equivalent to BSC); M100: No→ Yes; M130: No→Yes; M146: [redacted]→1; M147: [redacted]→1; M148: [redacted]→1; M163:M165: No→Yes; M191: No→Yes; M198: [redacted]→1
Scenario D: As per Scenario C, + M264: [redacted]→ 1; M265: [redacted]→1
Scenario E: As per Scenario D, + Model settings H15: 30→1; Clinical inputs: M270 & M271→ set to 0%

5.2.3 EAG's exploratory and preferred analyses (PPF)

Table 44 details the results of the EAG preferred assumptions for PPF. The rationale behind the scenario analyses is similar provided in Section 5.2.2 above. Figures 18 and 19 illustrate the EAG preferred probabilistic results and Table 45 applies additional scenario analyses to the EAG preferred base case analysis for PPF.

Table 44 Impact of EAG preferred assumptions on the ICER (PPF)

Comparator	Total costs (£)	Total Lys	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
Company base case analysis						
NERA 18 mg	[redacted]	5.74	4.12			
BSC	[redacted]	4.65	3.32	[redacted]	0.80	[redacted]
NDB	[redacted]	5.09	3.65	[redacted]	0.47	[redacted]
Scenario 1 – Apply rate ratio from NMR for NDB health state transition probabilities (Rate ratio: Nera 18mg vs. NDB: 1.088)						
NERA 18 mg	[redacted]	5.74	4.12			
BSC	[redacted]	4.65	3.32	[redacted]	0.80	[redacted]
NDB	[redacted]	5.09	3.66	[redacted]	0.46	[redacted]
Scenario 2 – Apply Treatment discontinuation HR from NMR for nerandomilast 18mg vs. NDB ([redacted])						
NERA 18 mg	[redacted]	5.74	4.12			
BSC	[redacted]	4.65	3.32	[redacted]	0.80	[redacted]
NDB	[redacted]	5.09	3.65	[redacted]	0.47	[redacted]
Scenario 3 – remove company's continued treatment benefit post discontinuation assumption						

Comparator	Total costs (£)	Total Lys	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
NERA 18 mg	[redacted]	5.33	3.83			
BSC	[redacted]	4.65	3.32	[redacted]	0.51	[redacted]
NDB	[redacted]	4.89	3.50	[redacted]	0.33	[redacted]
Scenario 4 – Apply EAG correction to application of acute exacerbation disutilities						
NERA 18 mg	[redacted]	5.74	4.11			
BSC	[redacted]	4.65	3.31	[redacted]	0.80	[redacted]
NDB	[redacted]	5.09	3.64	[redacted]	0.47	[redacted]
Scenario 5 (remove liver function test disutility)						
NERA 18 mg	[redacted]	5.74	4.12			
BSC	[redacted]	4.65	3.32	[redacted]	0.80	[redacted]
NDB	[redacted]	5.09	3.66	[redacted]	0.46	[redacted]
Scenario 6 - Apply EAG preferred AE assumptions (include GI perforation, rescale utility values and apply corrected NHS reference costs)						
NERA 18 mg	[redacted]	5.74	4.12			
BSC	[redacted]	4.65	3.32	[redacted]	0.80	[redacted]
NDB	[redacted]	5.09	3.65	[redacted]	0.47	[redacted]
Scenario 7 – Apply corrected NHS reference costs for Physiotherapy and Occupational Therapy visits						
NERA 18 mg	[redacted]	5.74	4.12			
BSC	[redacted]	4.65	3.32	[redacted]	0.80	[redacted]

Comparator	Total costs (£)	Total Lys	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
NDB	[redacted]	5.09	3.65	[redacted]	0.47	[redacted]
EAG preferred base case analysis - deterministic (Scenarios 1-7 combined)						
NERA 18 mg	[redacted]	5.33	3.82			
BSC	[redacted]	4.65	3.31	[redacted]	0.51	[redacted]
NDB	[redacted]	4.89	3.51	[redacted]	0.31	[redacted]
EAG preferred base case analysis - probabilistic						
NERA 18 mg	[redacted]	5.36	3.81			
BSC	[redacted]	4.69	3.31	[redacted]	0.50	[redacted]
NDB	[redacted]	4.92	3.50	[redacted]	0.31	[redacted]



Figure 18 Incremental cost-effectiveness plane for EAG base case (PPF)



Figure 19 Cost-effectiveness acceptability curve for EAG base case (PPF)

Table 45 Additional scenario analyses undertaken by the EAG, applied to the EAG preferred base case (PPF).

Comparator	Total costs	Total Lys	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
EAG preferred base case analysis						
NERA 18 mg	[redacted]	5.33	3.82			
BSC	[redacted]	4.65	3.31	[redacted]	0.51	[redacted]
NDB	[redacted]	4.89	3.51	[redacted]	0.31	[redacted]
Additional Scenario A – Remove NDB stopping rule for PPF						
NERA 18 mg	[redacted]	5.33	3.82			
BSC	[redacted]	4.65	3.31	[redacted]	0.51	[redacted]
NDB	[redacted]	5.01	3.59	[redacted]	0.23	[redacted]
Scenarios assuming equivalence of clinical outcomes across active treatment arms						
Additional Scenario B – Assume all active treatments are equivalent on all outcomes except mortality and treatment discontinuation						
NERA 18 mg	[redacted]	5.33	3.82			
BSC	[redacted]	4.65	3.31	[redacted]	0.51	[redacted]
NDB	[redacted]	4.89	3.50	[redacted]	0.32	[redacted]
Additional Scenario C – Assume equivalence of all active treatments for transition probabilities, acute exacerbation and mortality (equal to BSC); allow differences in time to treatment discontinuation [A,B]						
NERA 18 mg	[redacted]	4.65	3.31			
NDB	[redacted]	4.65	3.31	[redacted]	-	-

Comparator	Total costs	Total Lys	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (Nera 18mg vs. comp)
Additional Scenario D – Assume equivalence of all active treatments for transition probabilities, acute exacerbation and mortality; all treatment discontinuation curves = nerandomilast [B]						
NERA 18 mg	[redacted]	4.65	3.31			
NDB	[redacted]	4.65	3.31	[redacted]	-	-
Additional Scenario E – Assume equivalence of all active treatments for transition probabilities, acute exacerbation and mortality and assume 1 year of treatment for all active comparators, no treatment discontinuation [B]						
NERA 18 mg	[redacted]	0.95	0.86			
NDB	[redacted]	0.95	0.86	[redacted]	-	-

[A] Achieved by setting all HRs in the model for FVC % predicted decline, acute exacerbation and mortality equal to 1 for NERA 18mg vs BSC using the NMA (i.e. all life year gains set equal to BSC). Risk of mortality HR for NDB vs NERA 18 mg also set to 1. NDB assumed equivalent to NERA 18 mg using the switches in the model for FVC % predicted decline and acute exacerbation. Switch must be also set to "Yes" for NERA 18 mg to use ITC results in each outcome. Essentially provides the results of a cost-comparison analysis amongst the active treatments.

[B] Implementation notes: Adaptations to 'clinical inputs' sheet, applied to EAG preferred base case model configuration:
Scenario C: Cell M27: No→Yes; M65: No→Yes; M130: No→Yes; M146: [redacted]→1; M147: [redacted]→1; M165: No→Yes; M191: No→Yes; M199: [redacted]→1.
Scenario D: As per Scenario C, + M264: [redacted]→ 1.
Scenario E: As per Scenario D, + Model settings H15: 34→1; Clinical inputs: M268 & M270→ set to 0%.

5.3 Decision modifiers

5.3.1 QALY weighting for severity

The EAG agrees with the company that QALY weighting is not relevant for this assessment. The EAG is satisfied that none of the scenarios explored in either the company or EAG analyses would qualify for QALY severity weightings.

5.3.2 Uncaptured benefits

The company submission proposes several uncaptured benefits of nerandomilast in the economic modelling. These are summarised below alongside the EAG's view and critique of the impact of those uncaptured benefits:

The company proposes that the model structure does not account for improvements in FVC % predicted state that were observed at early stages in the nerandomilast trials. Further information was provided in response to clarification queries.

The EAG has reviewed the data, and it is not clear to what extent any potential improvements in FVC% predicted state would differ between alternative active treatments. Whilst possible, the EAG does not consider the evidence to be sufficiently robust to enable an assessment of comparative gains in FVC% predicted states across the different active AF treatments considered in this appraisal.

The company suggests service benefits, for example non-inclusion of the need for liver function tests.

The EAG is satisfied that these costs are already considered within the economic modelling but accepts that any reduction in monitoring / testing requirements would have helpful capacity implications for NHS practice.

The company points to broader societal benefits of nerandomilast that are not included in the economic modelling, including caregiver burden and lost productivity from cessation of employment.

The EAG notes that the company have not chosen to included carer disutility in their economic modelling. The EAG accept that the condition likely impacts on carers but are unaware of any studies in this population that would provide a disutility for

application in the model. The EAG accepts the potential benefit of improved clinical outcomes vs. BSC on lost productivity and society more broadly. However, due to uncertainty surrounding the magnitude of clinical effectiveness benefit for nerandomilast over other active treatment comparators, it is unclear to what extent the treatment could deliver substantial societal benefits vs. currently available treatments.

The company notes that the economic model does not include lung transplantation and that stabilisation of disease with active treatments might facilitate lung transplantation in clinical practice.

As noted in response to an EAG clarification question on this issue, the company and EAG agree that there is uncertainty surrounding any potential treatment effect of nerandomilast on lung transplantation and it has therefore been excluded from the modelling.

5.3.3 Health inequalities

The company has not put forward any additional information for consideration with respect to how nerandomilast might help address health inequalities.

5.4 Confidential comparator and subsequent treatment prices

The EAG report has detailed all analyses with confidential commercial arrangements for both nerandomilast and nintedanib applied. Both nerandomilast and nintedanib discounts are included as they are both Boehringer Ingelheim products, hence their inclusion in the EAG report, and eMIT prices have been used for pirfenidone. Subsequent to the post FAC version of the EAG report, there have been updated commercial arrangements for the comparator, nintedanib. A confidential appendix is therefore included detailing all company and EAG conducted analyses with the updated commercial arrangements applied.

5.5 Conclusions of the cost-effectiveness section

The company has submitted a Markov cohort model for the assessment of Nerandomilast 18mg vs. BSC, Nintedanib and Pirfenidone for IPF and for the assessment of Nerandomilast 18mg. vs BSC and Nintedanib for PPF. The model assumes all active treatments are used as monotherapy. The main drivers of

incremental costs in the model are the treatment acquisition costs for nerandomilast, nintedanib and pirfenidone respectively. The main drivers of QALY gains are associated with modelled mortality benefits for nerandomilast 18mg vs. comparators. There are additionally some key areas of uncertainty that are not accounted for in the economic modelling which may have an important impact on the ICER. These primarily relate to treatment sequencing, and it has not been possible for the EAG to fully explore a plausible ICER including treatment sequencing due to a lack of available data for 2nd line AF treatment. The EAG considers the bias, on balance, to be in favour of nerandomilast due to adding additional treatment acquisition costs of further lines of treatment post discontinuation in the pathway for a world with compared to a world without nerandomilast. The additional QALY gains of subsequent lines of treatment are uncertain, but it is plausible to assume that a second line of treatment in a group of patients who have already experienced disease deterioration on an AF therapy would not be as effective as the treatments use in a broader cohort (i.e. those progressing on nerandomilast are potentially a harder to treat group, hence likely to have lower QALY gains for the additional costs incurred of further treatment lines post discontinuation.

There is also an issue of unresolved uncertainty surrounding the potential stopping rule for nintedanib for PPF, which has been included in the model, but is not explicitly recommended in the relevant NICE guidance. This likely biases against nerandomilast. The kay differences between the company and EAG preferred base case ICERs, which it has been possible for the EAG to explore in the model are as follows:

- The company prefers to assume equivalence between all active AF treatments in terms of health state transition probabilities, whereas the EAG prefers to use data from the NMR where available, and from the NMA for pirfenidone for IPF.

- The company assumes equivalence between PFN and NDB for several clinical effectiveness parameters whereas the EAG prefers to use the available data from the Bayesian NMA.

- The company prefers to apply an assumption of continued treatment effectiveness following discontinuation, based on time since treatment initiation, whereas the EAG prefer to assume treatment effectiveness is lost in the cycle following discontinuation. The EAG would welcome exploration of additional approaches to model reducing treatment effect for the full cohort.
- The EAG prefers to update some adverse event, cost and utility parameters in the model, but these have a comparatively minor impact on the ICER.

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SingleTechnology Appraisal

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis [ID6446]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on the date in the accompanying email** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 EAG key issue 1 (The company have not considered competing risks for clinical outcomes)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
External Assessment Group (EAG) description of key issue 1 states "However, it is plausible that failure to account for competing risks in the economic model could introduce substantial bias in the cost-effectiveness estimates".	Please re-word to: "However, it is plausible that failure to account for competing risks in the economic model could introduce bias in the cost-effectiveness estimates. The impact of this expected to be negligible".	The EAG note that as death is a competing risk, a competing risks analysis could have been applied for non-fatal events. Within the economic model, this is only relevant for rates of acute exacerbations. Scenario analyses included in the company submission demonstrated that alternative assumptions for rates of acute exacerbations have a negligible impact on cost-effectiveness results. As such, a differing statistical approach for rates of acute exacerbations is not expected to materially impact the results of the economic evaluation.	The text has been updated to remove the word 'substantial' and to provide an additional sentence explaining why the magnitude of bias associated with acute exacerbation parameterisation is expected to be small.

Issue 2 EAG key issue 2 (No significant effects in most comparisons)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG description of key issue 2 on page 6 states that "The ITC analyses did not show any significant difference between nerandomilast and nintedanib and pirfenidone".	Suggestion to re-word to: "The ITC analyses did not show any statistically significant difference between nerandomilast and nintedanib and pirfenidone in most efficacy endpoints, while showing statistically significant differences in time to treatment discontinuation (TTD) and several safety outcomes. This is largely due to small sample size in monotherapy subgroups of FIBRONEER trials. It is also consistent with prior NICE TAs in IPF and PPF, where non-significant mortality improvements were accepted as suitable to inform decision-making. While the difference in mortality between nerandomilast and	The lack of statistical significance in the individual patient data (IPD) meta-regression analyses conducted separately for idiopathic pulmonary fibrosis (IPF) (FIBRONEER-IPF and INPULSIS-1 and -2) and progressive pulmonary fibrosis (PPF) (FIBRONEER-ILD and INBUILD) was largely due to the small size of 'no background AF' cohorts in the FIBRONEER trials – the indirect treatment comparison (ITC) results of pooled IPF and PPF data (FIBRONEER-IPF + FIBRONEER-ILD + INPULSIS-1 + INPULSIS-2 + INBUILD), which increase the sample size, show statistically significant reduction in mortality for nerandomilast vs nintedanib in pulmonary fibrosis (adjusted hazard ratio [HR] for time to death over the whole trial, [redacted] [95% confidence interval (CI), [redacted]]; p = 0.007). See Figure 1 and Appendix 1 for the full results of the pooled IPD meta-regression. This demonstrates the robust and statistically significant benefit of nerandomilast on reducing the risk of death in patients with IPF and PPF.	While the EAG accepts that statistically significant differences were observed for a small number of exploratory outcomes, these were not the primary outcomes used to assess treatment effectiveness. The company suggests that the lack of statistically significant effects for the main outcomes may be due to small sample sizes. However, this explanation does not increase certainty in the reported results. The wording has therefore been updated to reflect that the ITC did not show

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	nintedanib was not statistically significant, it was found to be clinically meaningful by clinicians".	*Figure 1. Cumulative incidence plot for the risk of death, IPD meta-regression, pooled IPF and PPF data*  Key: NDB, nintedanib; NERA, nerandomilast. Importantly, while the separate IPF and PPF ITC analyses did not demonstrate statistically significant differences for the key efficacy endpoints (as mentioned above, largely due to the relatively small sample sizes in the FIBRONEER monotherapy subgroups), clinicians considered the magnitude and direction of the observed treatment effects to be clinically meaningful. This is particularly relevant because survival outcomes in IPF	any statistically significant differences in the main effectiveness outcomes.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		and PPF remain poor, and are worse than those observed in several common cancers, underscoring the severity and life-limiting nature of these conditions.[1] Accordingly, there is a clear and urgent unmet need for new treatment options that are effective, safe, and well tolerated, and that can slow disease progression, extend survival, and preserve patients' overall health-related quality of life (HRQoL). Importantly, the FIBRONEER trials are the first randomised controlled trials (RCTs) in IPF and PPF to report nominally significant overall survival (OS) differences vs best supportive care (BSC). In addition, non-significant OS benefits have previously been accepted by National Institute for Health and Care Excellence (NICE) Committees in prior appraisals of antifibrotics (AFs) in IPF and PPF.[2-5] Using non-significant OS estimates from the ITC is consistent with the general principle of incorporating all available evidence and reflecting uncertainty within probabilistic sensitivity analyses (PSAs). As the EAG later states: "The EAG therefore considers it more	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		appropriate to make the best use of the available data, using the results from the meta-regression and NMA for the base case analysis". It should also be noted that the statement "The ITC analyses did not show any significant difference between nerandomilast and nintedanib and pirfenidone" is factually incorrect, as statistically significant differences (in separate ITCs for IPF and PPF) were observed for time to treatment discontinuation (TTD) and for several safety endpoints in favour of nerandomilast (see Table 26 in Company Submission). In conclusion, nerandomilast shows clinically meaningful reduction in the risk of death compared with nintedanib in both IPF and PPF, which reaches statistical significance in the pooled IPF + PPF ITC analyses.	
EAG description of key issue 2 on page 6 states that "In the absence of a robust treatment effect on clinical outcomes, the EAG considers that the	Please remove this statement.	As explained above, comparison based solely on costs is not appropriate due to nerandomilast showing clinically meaningful reduction in the risk of death compared with nintedanib in both IPF and PPF, which reaches statistical significance in pooled IPF	The EAG agrees that the uncertainty surrounding the effect estimates should be included in the base case analyses. The

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
committee may wish to consider a comparison focused solely on costs".		+ PPF ITC analyses (HR for time to death over the whole trial, [redacted]. Differences in TTD and some safety endpoints show statistically significant benefit for nerandomilast over nintedanib in the individual IPF and PPF ITCs, which are also important clinical outcomes. Using non-significant OS estimates from the ITC is consistent with the general principle of incorporating all available evidence and reflecting uncertainty within PSA, and this approach has previously been accepted in other technology appraisals (TAs) in IPF and PPF.[2-5]	EAG has applied this assumption consistently across all outcomes and all treatment alternatives. The text has been amended to clarify the EAG's preferred position, noting that equivalence assumptions are included only as scenario analyses. The leading statement related to committee consideration has also been removed.

Issue 3 EAG key issue 3 (Uncertainty regarding the continued duration of treatment benefit after treatment discontinuation)

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr>
<td>On page 88, the EAG report states that “discontinuation only impacts on treatment specific mortality or %FVC health state outcomes after cycle [redacted] (IPF) or cycle [redacted] (PPF)”.

This does not acknowledge that the impact of discontinuation is already accounted for within analyses of the observed FIBRONEER data, as patients who discontinued study medication were not censored from</td>
<td>We propose amending the text to:

“In addition to the impact of discontinuation observed in the FIBRONEER trials, which implicitly influences long-term estimates of efficacy (FVC decline, risk of acute exacerbation and mortality), the company implemented an additional explicit waning assumption after cycle [redacted] (IPF) or cycle [redacted] (PPF)”.</td>
<td>The current description of the EAG’s key issue 3 does not fully explain that that the FIBRONEER trial outcomes used in the cost-effectiveness model implicitly account for discontinuations which occur within the respective trial follow-up.

This is because patients who discontinued nerandomilast in the FIBRONEER trials were not censored, so their data were included in the modelled OS analyses, acute exacerbation analyses and FVC % predicted state outcomes.

Over the whole follow-up period of FIBRONEER-IPF up to database lock 2 (DBL2), among [redacted] patients who prematurely discontinued nerandomilast, there were no patients who were lost to follow up in the no background AF therapy subgroup (see Table 1 in Appendix 1: Pooled ITC results (IPD meta-regression based on FIBRONEER-IPF, FIBRONEER-ILD, INPULSIS-1, INPULSIS-2 and INBUILD trials)

<table>
<tr><th>Outcome</th></tr>
<tr><td>Time to death over the whole trial</td></tr>
<tr><td>Time to first progression over the whole trial</td></tr>
<tr><td>Time to first acute exacerbation over the whole trial</td></tr>
<tr><td>Time to treatment discontinuation over the whole trial</td></tr>
</table>
</td>
<td>This is not a factual inaccuracy. Pages 88 and 89 of the EAG report already acknowledge the company’s position. However, the EAG also acknowledges and</td>
</tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
OS analyses. That is, the Kaplan–Meir plot of OS FIBRONEER data used to inform survival modelling included patients who discontinued nerandomilast between treatment initiation (cycle 0 in the model) and the end of follow-up in FIBRONEER trials (cycle [redacted] for IPF and cycle [redacted] for PPF). Because of this, the impact of treatment discontinuation on clinical outcomes (forced vital capacity [FVC] decline, risk of acute exacerbation and mortality) is		**CFB in FVC percent predicted at 52 weeks** **CFB in FVC (mL) at 52 weeks** **Time to respiratory related death over the whole trial** **Rate of progression over the whole trial** **Proportion of patients with progression over the whole trial** **Proportion of patients experiencing acute exacerbation over the whole trial** **Proportion of patients experiencing death over the whole trial** **Proportion of patients experiencing respiratory-related death over the whole trial** **Proportion of patients experiencing serious AE** **Proportion of patients experiencing diarrhea over the whole trial** **Proportion of patients experiencing GI disorders over the whole trial** **Proportion of patients with study discontinuation** **Proportion of patients with treatment discontinuation** **Proportion of patients with treatment discontinuation due to AE** **Key:** AE, adverse event; CFB, change from baseline; CI, confidence interval; FVC, forced difference; OR, odds ratio; RR, rate ratio.	welcomes the additional information provided by the company in Appendix 3. As noted in Issue 3 of the EAG report, the EAG would welcome scenario analyses exploring alternative G

<table>
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<tr><td>already included within the trial and so will be implicitly propagated into their extrapolations. Because efficacy outcomes already reflect the impact of discontinuation during the trial, the company assumption that efficacy outcomes are further waned due to treatment discontinuations 1 year after the end of trial follow-up is already very conservative. Hence, any scenarios should explore longer times before incorporating</td><td></td><td>Appendix 2: FIBRONEER trials – premature discontinuation data).[6]

Similarly, over the whole follow-up period of FIBRONEER-ILD up to DBL2, among [redacted] patients who prematurely discontinued nerandomilast, there were no patients who were lost to follow up in the no background AF therapy subgroup (see Table 2 in Appendix 1: Pooled ITC results (IPD meta-regression based on FIBRONEER-IPF, FIBRONEER-ILD, INPULSIS-1, INPULSIS-2 and INBUILD trials)
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<tr><td>CFB in FVC (mL) at 52 weeks</td></tr>
<tr><td>Time to respiratory related death over the whole trial</td></tr>
<tr><td>Rate of progression over the whole trial</td></tr>
<tr><td>Proportion of patients with progression over the whole trial</td></tr>
<tr><td>Proportion of patients experiencing acute exacerbation over the whole trial</td></tr>
<tr><td>Proportion of patients experiencing death over the whole trial</td></tr>
</table></td><td>methods for implementing the treatment waning assumption in the model.</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
waning to BSC outcomes following treatment discontinuation. We therefore consider that the approach taken by the EAG in scenario 7 (IPF) and scenario 3 (PPF) is effectively double-counting the impact of discontinuation on the nerandomilast modelled outcomes during the time period of the FIBRONEER trials.		**Proportion of patients experiencing respiratory-related death over the whole trial** **Proportion of patients experiencing serious AE** **Proportion of patients experiencing diarrhea over the whole trial** **Proportion of patients experiencing GI disorders over the whole trial** **Proportion of patients with study discontinuation** **Proportion of patients with treatment discontinuation** **Proportion of patients with treatment discontinuation due to AE** **Key:** AE, adverse event; CFB, change from baseline; CI, confidence interval; FVC, forced difference; OR, odds ratio; RR, rate ratio. Appendix 2: FIBRONEER trials – premature discontinuation data).[7] As such, an assumption that no treatment effect is retained after discontinuation before the end of the trial follow-up is implausible as it double-counts the impact of discontinuation implicitly observed in the trial data by combining it with an explicitly modelled treatment effect waning. It should also be noted that the survival curve selected in both the company and EAG base case (gamma curve for both) assumes an increasing hazard rate over time, so regardless of the inclusion of a	G

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		treatment effect waning assumption, the treatment effect of nerandomilast inherently cannot be constant over time (see Appendix 3). Furthermore, the company has formally elicited estimates of OS from UK clinicians and has provided these for comparison with modelled OS under base-case and exploratory assumptions. These estimates highlight that the base-case waning assumption is highly conservative in PPF and aligns with expert beliefs in IPF – see Appendix 3. In fact, OS outputs assuming 50-year treatment effect waning are best aligned with structured expert elicitation (SEE) clinical validation outputs in PPF. Importantly, no treatment waning assumptions were employed in prior appraisals of nintedanib in IPF and PPF (TA379[3], TA864[4], TA747[5]); while 5-year treatment waning has previously been accepted for pirfenidone in TA504.[2] Therefore, the approaches suggested by the EAG are inconsistent with previous TAs.	
On page 7, the EAG states: "The company preferred approach assumes that there is a continued treatment effect of active treatments	We propose amending to: "The company preferred approach assumes that there is a continued modelled treatment effect of active	As above, the company's base-case approach does not assume continued treatment effects in the cost-effectiveness model, which is a conservative assumption – during SEE, clinical experts indicated that they expect the treatment effect may persist for 3–6 months after discontinuation; this is not currently implemented in the model. Instead, patients who discontinue nerandomilast (beyond the initial time corresponding to trial follow-up plus 1 year to avoid double-counting any effects of discontinuations observed during the trial) immediately move to BSC outcomes.	This is not a factual inaccuracy. The justification for the company

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
following treatment discontinuation, based on time since treatment initiation". Without additional explanation, this statement is at risk of being misinterpreted.	treatments following treatment discontinuation until 1 year after trial follow-up. This is because efficacy outcomes for those who remain on treatment are based on the overall trial outcomes, which include the impact of treatment discontinuation; hence, for consistency the overall trial outcomes are also assumed to apply to patients who discontinue treatment. This is conservatively		's preferred approach is acknowledged on pages 88-89 of the EAG report. The statement in the executive summary has been updated to specify the duration after trial follow-up for which the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	assumed to last for 1 year after trial follow-up. After this point, the modelled trial outcomes are lost immediately upon discontinuation".		assumption is applied.
On page 7, the EAG states: "The EAG accepts that there may also be treatment waning whilst on active treatments and this has not been explored".	Remove this statement.	As stated above, the use of increasing hazards for mortality demonstrates that the treatment effect is not constant over time. In addition, as more patients discontinue treatment, the overall outcomes for active treatments are explicitly waned to the outcomes for BSC. Hence, the economic model already incorporates treatment waning.	This is not a factual inaccuracy. The company has not applied treatment-effect waning over extrapolation in

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			the economic model for the proportion of the cohort that is modelled to remain on treatment in the long term. The EAG also notes that for mortality outcomes, treatmen

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			t effect estimates included in the model are assumed to be constant over time (i.e. proportional hazards is assumed to hold).
On page 89, the EAG states: “A more appropriate, and in the EAG’s view, less biased approach would have been to	Remove this statement.	The current approach to modelling loss of treatment effectiveness is an implementation of treatment waning; the time-of-onset is measured relative to model start, with the waning-weight equal to the proportion of patients who discontinue. Graphs presenting the modelled mortality hazard over time are presented in Appendix 3. These highlight that the nerandomilast hazards converge to the BSC hazards over time, reflecting gradual treatment effect waning.	Not a factual inaccuracy. However, the EAG

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
explore the impact of loss in treatment effect over time directly on the treatment effectiveness extrapolation curves…" This statement is at risk of being misinterpreted and does not accurately reflect the modelling approach taken by the company.			acknowledges the additional information provided in Appendix 3 of this factual accuracy check.
On page 89, the EAG states: "As the EAG does not have access to the underlying data	We propose amending this to: "As the EAG does not have access to the underlying data	Survival curves with increasing HRs over time are used in the company base-case approach with the adjustment for treatment discontinuation ensuring that hazards in all active treatment arms converge with BSC hazards over time as patients discontinue treatment. As noted above, the	The EAG welcomes the additional informati

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
from the company's IPD analysis, it was not possible to explore the impact of independently fitted survival curves, with reducing HRs over time, on the ICER". This statement is at risk of being misinterpreted and does not accurately reflect that the survival curves used in the company base-case approach assume increasing HRs over time.	from the company's IPD analysis, it was not possible to explore alternative implementation of treatment waning, including use of independently fitted survival curves".	nerandomilast mortality hazards converge to the BSC hazards over time, which reflects gradual treatment effect waning (see Appendix 3).	on in Appendix 3. The statement in the EAG report remains valid but has been revised, as requested, to avoid misinterpretation.
Page 90, Table 22	Please amend to:	The description of the Company's approach may be misinterpreted to mean that only patients who are off treatment at [redacted] and [redacted] years post treatment initiation are assumed to have lost treatment effect.	This is not a factual inaccura

Description of problem		Description of proposed amendment		Justification for amendment	EAG response
Parameter / Assumption	**Company approach**	**Parameter / Assumption**	**Company approach**		
Company approach	Transition probabilities and mortality effect sizes switched from active treatment to BSC arm for 'off treatme	Company approach	Transition probabilities and mortality effect sizes switched from active treatment to BSC arm for 'off treatme	The EAG's proposed alternative scenario 1 is not materially different to the approach adopted in the company base case, as illustrated in the graphs showing mortality hazards over time (presented in Appendix 3).	cy; the similarity is already noted in Table 22. However, the text has been revised to reflect the EAGs suggestion more accurately.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
nt' proportion of the cohort after [redacted] and [redacted] years post treatment initiation for IPF and PPF respectively (based on 1 year post	nt' proportion of the cohort in each model cycle after [redacted] and [redacted] years post treatment initiation for IPF and PPF, respectively (based		

Description of problem		Description of proposed amendment		Justification for amendment	EAG response
	end of follow up from FIBRONEER trials)		on [redacted] post end of follow-up from FIBRONEER trials)		
Company scenarios	Scenarios explored 5 and 50 years with the latter retaining treatment effectiveness for the whole	Company scenarios	Scenarios explored 5 and 50 years, with the latter retaining treatment effectiveness		

Description of problem		Description of proposed amendment		Justification for amendment	EAG response
	cohort as per the projected extrapolation curves		for the whole cohort as per the projected extrapolation curves		
EAG alternative scenario suggestion 1	As per company scenario, but apply adjustment to HRs to allow convergence over time	EAG alternative scenario suggestion 1	Switch transitions to BSC immediately at the point of treatment discontinuation		

Description of problem		Description of proposed amendment	Justification for amendment	EAG response
EAG alternative scenario suggestion 2	Switch transitions to BSC immediately at the point of treatment discontinuation			
On page 90, the EAG states: "Treatment discontinuation is modelled and the company model includes an approach to model treatment waning effects in the 'off treatment' cohort,		Please amend to: "Treatment discontinuation is modelled and the company model includes an approach to model treatment waning effects in the 'off treatment' cohort, based on time	The Company's preferred base-case effect waning assumption incorporates the impact of time at discontinuation for all patients modelled as discontinuing after the cut-off of trial follow-up + 1 year.	This is not a factual inaccuracy. No amendments have been made to

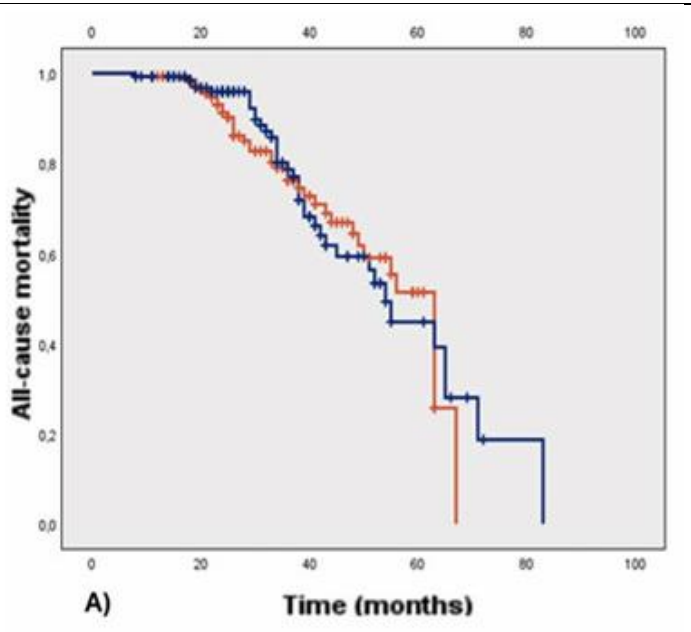
Description of problem	Description of proposed amendment	Justification for amendment	EAG response
based on time since treatment initiation".	since treatment initiation and time at discontinuation".		the EAG report.
On page 91, the EAG states: "The company prefers to apply treatment waning effects that are based on time since treatment initiation for the 'off treatment' proportion of the cohort".	Please amend to: "The company prefers to apply treatment waning effects that are based on time since treatment initiation and time at treatment discontinuation for the 'off treatment' proportion of the cohort".	The Company's preferred approach incorporates both time since treatment initiation and time at discontinuation.	This is not a factual inaccuracy. No amendments have been made to the EAG report.
On page 3, the EAG states: "The company prefers to apply an	Please amend to: "The company prefers to use the observed overall	The Company's preferred approach is conservative and includes consideration of time at discontinuation (see above for details).	The EAG notes the company's justificati

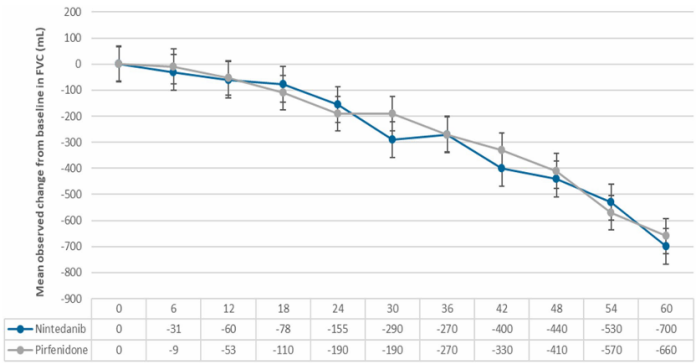
Description of problem	Description of proposed amendment	Justification for amendment	EAG response
assumption of continued treatment effectiveness following discontinuation, based on time since treatment initiation,"	trial outcomes, which include the impact of treatment discontinuation. To avoid double-counting, a conservative assumption of continued modelled treatment effectiveness following discontinuation, for up to 1 year after the end of trial follow-up, is included. Following that period, people who discontinue nerandomilast immediately move to BSC outcomes".		on. However, the EAG does not consider this to be a factual inaccuracy. Several updates have been made in response to the issues raised above, which the EAG hopes clarify its position.

Issue 4 EAG key issue 4 (Most appropriate sources of relative treatment benefit for the economic model for pirfenidone in IPF)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In description of key issue 4, the EAG states it prefers to make use of the best available data, prioritising data from the network meta-analysis (NMA) to estimate relative treatment effect sizes for nerandomilast 18 mg vs pirfenidone overusing estimates from more methodologically robust IPD meta-regression analyses; assuming equal efficacy between pirfenidone and nintedanib.	Suggested amendment: "The company have raised concerns about the limitations of the NMA based on the fact that the lack of population adjustments can lead to confounding of the results. However, the EAG..."	Assumption of equal efficacy between nintedanib and pirfenidone has been thoroughly validated using a variety of sources, and allows for the use of the most methodologically robust evidence available (population-adjusted IPD meta-regression). The following support the similar efficacy of nintedanib and pirfenidone: - NICE Committee decision in TA379, which used an odds ratio of 1 when comparing OS for nintedanib and pirfenidone, stating that "[the Committee] considered the effectiveness of nintedanib and discussed the results of the company NMA and concluded that the clinical effectiveness of nintedanib is similar to pirfenidone".[3] - The opinion of clinical experts, who perceive both AFs as having broadly similar efficacy for the treatment of IPF.[8, 9]	This is not a factual inaccuracy. The company's description of the problem misrepresents the EAG's position. The EAG base case analyses use the results of the NMR where possible, then apply the treatment effect sizes from the NMA only for pirfenidone. A scenario analysis explores the use of

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		- Results of six independently published ITCs (See Appendix 4): OR (95% CI) for nintedanib vs pirfenidone for decline ≥ 10 percentage points in FVC % predicted ranged from 0.98 (0.67, 1.42) to 1.14 (0.83, 1.67) across four ITCs; OR (95% CI) for death ranged from 1.02 (0.55, 1.87) to 1.10 (0.12, 10.00) across four ITCs; and RR was reported as 0.86 in one ITC. - An Italian real-world data study (n = 292 patients with IPF; mean follow-up time of 32.3 months [standard deviation (SD) = 14.5]) showing no difference in OS or FVC decline between nintedanib and pirfenidone.[10] - Additional real world studies corroborated findings of comparable mortality rates with nintedanib and pirfenidone[11-19] *Figure 2. Kaplan-Meier curves for all-cause mortality; nintedanib (orange) vs. pirfenidone (blue); crosses indicate censoring [Figure 2 in Lalla et al. 2025[10]]*	the NMA for all comparisons. The text has however been revised to acknowledge the company's position more fully.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		 *Figure 3. Change from Baseline in absolute Forced Vital Capacity (FVC) expressed in mL over 5 years of observation in patients treated with nintedanib and pirfenidone [Figure 3 in Lalla et al. 2025[10]]*	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		 In view of the above, it was considered appropriate to assume equal efficacy of nintedanib and pirfenidone, and apply IPD meta-regression outcomes for nerandomilast vs nintedanib to the comparison of nerandomilast vs pirfenidone. This allowed the use of the most methodologically robust method to inform comparative efficacy of nerandomilast and AFs. Conventional NMAs are limited in their ability to account for imbalances in baseline characteristics across trials. Such differences can introduce bias and lead to potentially misleading estimates of relative treatment effects. In this context, IPD meta-regression represents a more appropriate and methodologically robust	

	0	6	12	18	24	30	36	42	48	54	60
Nintedanib	0	-31	-60	-78	-155	-290	-270	-400	-440	-530	-700
Pirfenidone	0	-9	-53	-110	-190	-190	-270	-330	-410	-570	-660

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		approach, as it explicitly models heterogeneity and adjusts for patient-level covariates. This is also consistent with the EAG's own methodological view: the EAG agrees that, where IPD are available, meta-regression is the most robust approach for indirect comparison and should be preferred to aggregate-data methods. This is not a theoretical concern in this appraisal; the company has already highlighted that baseline differences between FIBRONEER and comparator trials mean unadjusted aggregate ITCs are likely confounded and should be interpreted with caution. The need for population adjustment is illustrated by the observed divergence between IPD-adjusted and unadjusted aggregate NMA estimates for key outcomes. For example, for the outcomes 'Absolute change from baseline in FVC (mL) at 52 weeks, mean difference' in the IPF population vs nintedanib 150 mg, the IPD meta-regression provides an estimate (95% CI) of [redacted] ([redacted]), whilst for the Bayesian NMA, the values are [redacted] ([redacted]). This illustrates the importance of population adjustment.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		It is also worth noting that HR (95% CrI) for time to death over the whole trial duration for nerandomilast 18 mg vs nintedanib 150 mg and nerandomilast 18 mg vs pirfenidone 801 mg were almost identical in both the Bucher ITC ([redacted] vs [redacted]) and the Bayesian NMA ([redacted] vs [redacted]). This illustrates that any differences in HRs for death for nerandomilast vs nintedanib (from IPD meta-regression) and nerandomilast vs pirfenidone stem from the confounding linked to lack of population adjustment in the aggregate ITC methods, rather than any true differences in relative efficacy of nerandomilast vs both AFs. In conclusion, by using IPD meta-regression estimates to inform relative efficacy of nerandomilast vs both nintedanib and pirfenidone, the company approach uses the most robust evidence available.	

Issue 5 EAG key issue 6 (Treatment sequencing)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 2, key issue 6 is labelled as having "Unknown, potentially large" impact on cost-effectiveness results. On page 81, the EAG states: "The EAG considers this to be an unresolved area of residual uncertainty for decision making that could have an important impact on the ICER".	We propose that the labelling of key issue 6 be changed to "unknown – potentially small". We propose that the wording in page 81 be modified to: "The EAG considers this to be an unresolved area of residual uncertainty for decision making that could have an **unclear and likely small** impact on the ICER".	The company agrees with the EAG that there is insufficient evidence to support a robust evaluation of effectiveness when modelled comparators are used as subsequent treatments (e.g. there are no sources of evidence which could inform the impact of subsequent AF use following discontinuation of nerandomilast in patients with IPF or PPF). We also acknowledge that there is uncertainty around the direction and magnitude of bias for cost-effectiveness. Consideration of AF use after patients discontinue nerandomilast or another AF should encompass both a corresponding clinical benefit and additional cost. The additional cost of subsequent AF use would be dependent on the proportion of patients discontinuing to subsequent therapy, the	This is not a factual inaccuracy. The impact of this issue on the ICER is unknown.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		distribution of those therapies and the duration of subsequent treatment. Whilst it is not possible to quantify the magnitude of these impacts, inclusion of treatment sequencing would likely benefit nerandomilast as it offers an additional active treatment option for patients who would otherwise receive BSC only. Additionally, including any additional benefit from subsequent pirfenidone use would be associated with minimal acquisition costs compared with the unquantified benefit in clinical outcomes when compared to BSC use. Therefore, whilst it is not possible to definitively state if including treatment sequences would be favourable or not to nerandomilast, it is anticipated that it would be favourable, but	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		with a minor impact. Hence the conservative suggested wording.	
On pages 3 and 152, the EAG states that inability to model treatment sequencing "likely biases in favour of nerandomilast".	We propose to adjust text on pages 3 and 152 to "This creates a bias of uncertain direction and magnitude for cost-effectiveness", consistent with the EAG report, page 10.	As noted above, there are numerous uncertainties around the impact of considering subsequent AF use in the cost-effectiveness analysis, as additional efficacy benefits from subsequent AFs after nerandomilast would need to be accounted for at limited increased cost, potentially benefitting the nerandomilast arm in a scenario where treatment sequencing was fully implemented. However, due to lack of evidence to robustly inform efficacy of AFs in second-line setting, the company is not able to reliably incorporate treatment sequencing into the model. This is also acknowledged by the EAG on pages 10 and 81.	This is not a factual inaccuracy. The EAG considers the bias, on balance, to favour nerandomilast, as the model adds further treatment acquisition costs for further lines of treatment after discontinuation in the pathway with nerandomilast compared with the pathway without nerandomilast. The QALY gains are uncertain. However, it is plausible that a second-line treatment used in a group of patients who have already progressed would be less effective than treatments used in a

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			broader cohort. Patients progressing on nerandomilast may represent a harder-to-treat group and may therefore be expected to have lower QALY gains for the additional costs incurred from subsequent treatment lines. Further text added to justify the EAG's position.
The expected effect on the cost-effectiveness estimates of key issue 6 on page 10 is described as: *"*The impact on the ICER of a modelling approach that may not reflect UK clinical practice in terms of treatment sequencing is unclear. Second line treatments would add additional treatment	We propose adjusting the text to: "Second line treatments would add additional treatment acquisition costs to the pathway for nerandomilast, nintedanib, and pirfenidone (IPF only) depending on which treatment is prescribed first in clinical practice; with the magnitude of QALY gains unknown".	As noted above, the impact on acquisition costs is dependent on the distribution of subsequent treatments, proportion of patients receiving second-line treatment and the duration of these treatments. As noted above, there is no evidence available to inform efficacy of second-line AFs and thus the magnitude of any	This is not a factual inaccuracy. See further detail added in the EAG amendment above.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
acquisition costs to the pathway, especially for nerandomilast, but the magnitude of QALY gains is unknown".		potential quality-adjusted life year (QALY) gains is unclear.	
The description of key issue 6 on page 10 reads: "The company base case analysis compares active treatments as monotherapies, with no potential to move to second line active AF treatments following a loss of treatment effectiveness. This creates a bias of uncertain direction and magnitude for cost-effectiveness".	We propose that the description of the issue on page 10 be changed to "The company base case analysis compares active treatments as monotherapies in line with the final scope issued by NICE…"	The company notes that the final scope issued by NICE[20] includes comparison to active treatments rather than sequences of active treatments. As such, it is outside the scope of this appraisal to use a sequence of AFs as a comparator, or to consider nerandomilast sequentially with AFs as an intervention. Therefore, any request for such analyses should be noted as out of scope for this appraisal. As noted previously, any discussion of the magnitude of effect should reflect that it is likely to be small, and direction of bias is unknown (although including treatment sequencing would likely	This is not a factual inaccuracy. The EAG's understanding of the NICE scope is that it does not preclude consideration of subsequent treatments following disease progression.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		benefit nerandomilast, as discussed above).	
On page 81, the EAG states: "The EAG's clinical expert, aligned with the company sought expert opinion, is that UK clinicians would want to provide alternative AF treatments post nerandomilast discontinuation". This misinterprets clinical opinion to the company; without additional context, this statement could be misinterpreted.	We propose the wording by modified to: "The EAG's clinical expert, aligned with the company sought expert opinion, is that UK clinicians would want to provide alternative AF treatments post nerandomilast discontinuation and provide nerandomilast as a subsequent treatment when alternative AF treatments are used first".	The EAG referred to the clinical opinion sought by the company and mentioned that UK clinicians would want to provide alternative AF treatments post nerandomilast discontinuation. This is accurate, but the EAG failed to mention that clinical experts also said that, in a scenario where existing AFs were used first, they would want to provide nerandomilast as a subsequent treatment. Therefore, we feel that the clinical opinion provided by the company has been inaccurately represented in the EAG report and the conclusions made by the EAG on the impact on the incremental cost-effectiveness ratio (ICER) are also inaccurate on that basis.	Text has been revised for clarity. However, the EAG does not consider the proposed amendment to materially impact on the conclusions about the impact on the ICER. If nerandomilast was found to be cost-effective, it would be available post alternative AF therapies. Nevertheless, for the assessment of cost-effectiveness, it is not appropriate to include nerandomilast in the comparator arm of the model (even as a subsequent treatment) because it is not currently available on the NHS.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 81, the EAG states: "The EAG note that including subsequent treatments would increase treatment acquisition costs substantially,"	Amend this to: "The EAG note that including subsequent treatments would increase treatment acquisition costs,"	It is not clear that treatment acquisition costs would necessarily increase 'substantially'. Costs are likely to be aligned to first-line acquisition costs (weighted by the proportion of patients who receive subsequent treatment), which are minimal in the pirfenidone arm. Combined with the unclear magnitude of the QALY gain, this further demonstrates any impact on cost-effectiveness is of uncertain direction and likely small. Furthermore, the inclusion of subsequent treatment costs would be relevant for all active treatments; hence, the impact on incremental costs is expected to be minor for these comparisons.	The text has been revised to further clarify the EAG's position.
On page 81, the EAG states: "and this increase would be higher in the nerandomilast	Remove this statement.	It is not possible to know whether the additional costs would be greater in the nerandomilast arm without knowing which AF is	This is not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
arm of the model, due to the availability of more treatment options, especially for IPF (where NDB and PFN would both be feasible subsequent treatments)".		mostly likely to be used as a second-line option. Importantly, any (likely small) increase in costs would need to be weighed against the corresponding QALY gain, the magnitude of which is unclear. As a result, the impact on cost-effectiveness estimates is uncertain in direction and likely small in magnitude.	The EAG has clearly outlined the uncertainty on pages 81-82 of the report.

Issue 6 Incorrect implementation of EAG changes in the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Some scenarios conducted by the EAG are incompletely described and the company was unable to replicate the EAG results - IPF: additional scenarios G–I - PPF: additional scenarios C–E	We ask that the EAG provide a replicable implementation note for each additional scenario, including: 1) A clear statement of whether the scenario is applied on top of the EAG base case	The EAG does not clearly document which model inputs (parameters, switches, and assumptions) were changed to implement these additional scenarios, nor whether they are applied on top of the EAG base case. This lack of detail	The EAG thanks the company for the thorough cross-check and has implemented several changes.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	2) A list of all parameters and switches that were adjusted for the scenario 3) The treatment that the values align to	prevented the company from replicating EAG results and makes it difficult to interpret the results in the EAG report. In addition, the implemented scenario settings by the EAG do not appear to match what the EAG describes in the report. The company completed their analysis using the definitions outlined by the EAG and could not replicate the same results. This should be resolved by the EAG providing a clear, replicable implementation note for each additional scenario (including whether it is layered on the base case, the full list of adjusted parameters/switches with before/after values, and how those values align to the relevant treatment/comparator).	The EAG clarifies that all scenarios are applied to the EAG's preferred base case, as indicated in the table titles. For IPF, the EAG agrees with the company's implementation of scenarios G and H; and for PPF, agrees with the company's implementation of scenarios C and D. Scenario I (IPF) and Scenario E (PPF) are slightly different

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			to the suggested values by the company.Full implementation notes have now been added as footnotes to Tables 43 and 45 to better describe how these analyses were implemented.
EAG report, page 143, Table 43: "Additional Scenario G – Assume equivalence of all active treatments for transition probabilities, acute exacerbation and mortality; allow differences in time to treatment discontinuation [B]" EAG report, page 148, Table 45:	Amend text to: "Additional Scenario G/C – **Using EAG base case**, assume equivalence of all active treatments for transition probabilities, acute exacerbation and mortality **(equal to BSC)**; allow differences in time to treatment discontinuation [B]"	See above.	Text has been updated as suggested. Reference to implementation notes has been added.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"Additional Scenario C – Assume equivalence of all active treatments for transition probabilities, acute exacerbation and mortality; allow differences in time to treatment discontinuation [B]"			
EAG report, page 143, Table 43 and page 148, Table 45: "[B] Achieved by setting all HRs in the model for mortality equal to 1 using the NMA (i.e. all life year gains set equal to BSC). Essentially provides the results of a cost-comparison analysis amongst the active treatments".	Amend text to: "[B] Achieved by setting all HRs in the model for **FVC % predicted decline, acute exacerbation and** mortality equal to 1 **for NERA 18mg vs BSC** using the NMA (i.e. all life year gains set equal to BSC). **Risk of mortality HR for NDB vs NERA 18 mg also set to 1. NDB and PFN assumed equivalent to NERA 18 mg using the switches in the model for FVC % predicted decline and acute exacerbation. Switch must be also set to "Yes" for NERA 18 mg to use ITC results in each outcome.** Essentially provides the results of a cost-comparison analysis amongst the active treatments".	See above.	The text has been updated as suggested. Reference to implementation notes has been added.

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG response</th></tr>
<tr><td></td><td>Note: for PPF table, remove PFN references.</td><td></td><td></td></tr>
<tr><td>EAG report, page 143, Table 43
Results of additional scenario G:
<table><tr><td>NERA 18 mg</td><td>[redacted]</td><td>4.46</td><td>3.40</td><td></td></tr><tr><td>NDB</td><td>[redacted]</td><td>4.46</td><td>3.40</td><td>[redacted]</td></tr><tr><td>PFN</td><td>[redacted]</td><td>4.46</td><td>3.40</td><td>[redacted]</td></tr></table>EAG report, page 148, Table 45
Results of additional scenario C:
<table><tr><td>NERA 18 mg</td><td>[redacted]</td><td>4.65</td><td>3.33</td><td></td></tr><tr><td>NDB</td><td>[redacted]</td><td>4.65</td><td>3.33</td><td>[redacted]</td></tr></table></td><td>Update results:
IPF:
<table><tr><td>NERA 18 mg</td><td>[redacted]</td><td>4.46</td><td>3.39</td><td></td></tr><tr><td>NDB</td><td>[redacted]</td><td>4.46</td><td>3.39</td><td>[redacted]</td></tr><tr><td>PFN</td><td>[redacted]</td><td>4.46</td><td>3.39</td><td>[redacted]</td></tr></table>PPF:
<table><tr><td>NERA 18 mg</td><td>[redacted]</td><td>4.65</td><td>3.31</td><td></td></tr><tr><td>NDB</td><td>[redacted]</td><td>4.65</td><td>3.31</td><td>[redacted]</td></tr></table></td><td>Results in the EAG report are not available from the cost-effectiveness model.</td><td>Table 43 additional scenario G has been updated as per the company’s proposed amendment.

Table 45, additional scenario C has been updated as per the company’s proposed amendment.</td></tr>
<tr><td>EAG report, page 143, Table 43
“Additional Scenario H – Assume equivalence of all active treatments</td><td>Amend text to:
“Additional Scenario H/D – Using EAG base case, assume equivalence</td><td>See above.</td><td>Updated description of the scenario application and</td></tr>
</table>

<table>
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<tr>
<td>for transition probabilities, acute exacerbation and mortality; all treatment discontinuation curves = nerandomilast”.

EAG report, page 149, Table 45

“Additional Scenario D – Assume equivalence of all active treatments for transition probabilities, acute exacerbation and mortality; all treatment discontinuation curves = nerandomilast”.</td>
<td>of all active treatments for transition probabilities, acute exacerbation and mortality (equal to BSC); all treatment discontinuation curves = nerandomilast [C]”

Add to legend:

“[C] Using the same HR updates as Scenarios C and G, with further adjustments to treatment discontinuation by setting the HR for NDB vs NERA 18 mg and PFN vs NERA 18 mg to 1”

Note: for PPF table, remove PFN references.</td>
<td></td>
<td>implementation notes have been added as footnotes to Tables 43 and 45.</td>
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<tr>
<td>EAG report, page 143, Table 43

Results of additional scenario H:

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<tr><td>NDB</td><td>[redacted]</td><td>4.46</td><td>3.40</td><td>[redacted]</td></tr>
<tr><td>PFN</td><td>[redacted]</td><td>4.46</td><td>3.40</td><td>[redacted]</td></tr>
</table>
</td>
<td>Update results:

IPF:

<table>
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<tr><td>NDB</td><td>[redacted]</td><td>4.46</td><td>3.39</td><td>[redacted]</td></tr>
<tr><td>PFN</td><td>[redacted]</td><td>4.46</td><td>3.39</td><td>[redacted]</td></tr>
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PPF:</td>
<td>Results in the EAG report are not available from the cost-effectiveness model.</td>
<td>Table 43, additional scenario H has been updated as per the company’s</td>
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Results of additional scenario D:<table><tr><td>NERA 18 mg</td><td>[redacted]</td><td>4.65</td><td>3.33</td><td></td></tr><tr><td>NDB</td><td>[redacted]</td><td>4.65</td><td>3.33</td><td>[redacted]</td></tr></table></td>
<td><table><tr><td>NERA 18 mg</td><td>[redacted]</td><td>4.65</td><td>3.31</td><td></td></tr><tr><td>NDB</td><td>[redacted]</td><td>4.65</td><td>3.31</td><td>[redacted]</td></tr></table></td>
<td></td>
<td>proposed amendment.

Table 45, additional scenario D has been updated as per the company’s proposed amendment.</td>
</tr>
<tr>
<td>EAG report, page 143, Table 43:
“Additional Scenario I – Assume 1 year of treatment for all active comparators, no treatment discontinuation”
EAG report, page 149, Table 45:
“Additional Scenario E – Assume 1 year of treatment for all active comparators, no treatment discontinuation”</td>
<td>Amend text to:
“Additional Scenario I/E – Additional Scenario H/D, restricted to 1 year of treatment for all active comparators, no treatment discontinuation[D]”
Add to legend:
“[D] Uses the same as inputs as additional scenario H/D and restricts the treatment duration to 1 year. Treatment waning set to 50 years”.</td>
<td>See above.</td>
<td>Updated description of the scenario application and implementation notes have been added as footnotes to Tables 43 and 45.</td>
</tr>
</table>

<table>
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<tr>
<td>EAG report, page 143, Table 43
Results of additional scenario I:
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Results of additional scenario E:
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<td>Update results:
IPF:
<table><tr><td>NERA 18 mg</td><td>[redacted]</td><td>0.96</td><td>0.90</td><td></td></tr><tr><td>NDB</td><td>[redacted]</td><td>0.96</td><td>0.90</td><td>[redacted]</td></tr><tr><td>PFN</td><td>[redacted]</td><td>0.96</td><td>0.90</td><td>[redacted]</td></tr></table>PPF:
<table><tr><td>NERA 18 mg</td><td>[redacted]</td><td>0.95</td><td>0.86</td><td></td></tr><tr><td>NDB</td><td>[redacted]</td><td>0.95</td><td>0.86</td><td>[redacted]</td></tr></table></td>
<td>Results in the EAG report are not available from the cost-effectiveness model.</td>
<td>Table 43, additional scenario I has been updated as per the EAG’s implementation note.

Table 45, additional scenario E has been updated as per the EAG’s implementation note.</td>
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Issue 7 Incorrect statements

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.5 (Executive Summary), page 12, Table 2, and Section 5.2.2, page 136, Table 42: "Scenario 6 – As per scenario 7 + Apply Treatment discontinuation OR from NMA for nerandomilast 18mg vs. PFN ([redacted]) [B]"	Amend text to: "Scenario 6 – **As per scenario 5** + Apply Treatment discontinuation OR from NMA for nerandomilast 18 mg vs PFN ([redacted]) [B]"	Minor edit to note correct scenario number.	Scenario labelling has been revised as requested.
Section 5.5 (Executive Summary), page 14, Table 3: "Table 3 EAG preferred assumptions and ICER pairwise Nerandomilast vs. comparator (IPF)"	Amend text to: "Table 3 EAG preferred assumptions and ICER pairwise nerandomilast vs comparator **(PPF)**"	Minor edit to update to correct population.	Text and list of tables have been revised to correct this typographical error.
Section 2.2, page 17: "Nerandomilast is intended as a monotherapy and is not meant to replace existing AF therapies".	Remove the following wording from the following statement: "Nerandomilast is intended as a monotherapy ~~**and is not meant to replace existing AF therapies**~~".	Nerandomilast monotherapy could potentially be used at the same position as AF therapies, or after their failure as described in Section 1.3.4.3 of the company submission.	Text has been amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3, Table 4, page 22: "The anticipated date of UK regulatory approval is [redacted]"	Amend text to: "The anticipated date of UK regulatory approval is [redacted] 2026".	Anticipated Medicines and Healthcare products Regulatory Agency approval date has changed.	While this is outside the scope of the Factual Accuracy Check, we have updated the text as requested.
Section 3.2.1, page 28: "In the FIBRONEER-ILD study, 1,780 patients with PPF were randomised similarly".	Amend text to: "In the FIBRONEER-ILD study, **1,178** patients with PPF were randomised similarly…".	Minor edit – incorrect number of randomised patients for FIBRONEER-ILD.	Text has been amended as requested.
Section 3.2.2, page 36: "Secondary endpoints: Time to the first occurrence of acute idiopathic pulmonary fibrosis exacerbation, first hospitalisation for respiratory cause or death over the duration of the trial".	Amend text to: "Secondary endpoints: Time to the first occurrence of acute IPF**/ILD** exacerbation, first hospitalisation for respiratory cause or death over the duration of the trial".	Minor edit to ensure the common secondary endpoint title between IPF and ILD data includes both IPF and ILD exacerbation.	Text has been amended as requested.
Section 3.2.4, page 42: "The proportion of psychiatric disorder events	Amend text to: "The proportion of psychiatric disorder events at the **System**	Minor edit. Incorrect data point for FIBRONEER-IPF placebo arm as	The text for the SOC has been amended to correct this error.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
at the Social Organ Class (SOC) level was higher with 18 mg BID than with placebo at DBL2 in both trials (FIBRONEER-IPF: [redacted]; FIBRONEER-ILD: [redacted] ; Table 24 of the CS)".	Organ Class (SOC) level was higher with 18 mg BID than with placebo at DBL2 in both trials (FIBRONEER-IPF: [redacted] FIBRONEER-ILD: [redacted] Table 24 of the CS)…"	per company submission (CS) and original source.	Please note that the EAG cited Table 24 of the CS as the source of data for the proportion of psychiatric disorders in FIBRONEER-IPF, which reports values of [redacted]. However, Table 17 of the Appendix reports values of [redacted] . No changes were made to the values in the EAG report.
Section 3.2.2, page 36, page 37, page 49 and page 50 "Of the individual components of the key secondary endpoint, there was a significant benefit in the time to death for nerandomilast 18 mg bid compared with placebo (HR: [redacted])".	Amend text to: "Of the individual components of the key secondary endpoint, there was a **nominally** significant benefit in the time to death for nerandomilast 18 mg bid compared with placebo (HR: [redacted])".	No adjustment for multiplicity was planned beyond primary and key secondary objectives on DBL1. All other secondary endpoints conducted on DBL1, and all analyses conducted on DBL2 data are therefore considered exploratory in nature.	While the proposed addition of the word "nominally" may be intended as a qualifier of the statistical significance, the EAG does not consider this to be a factual inaccuracy. Therefore, no change has been made to the text of the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"Among the individual components of the key secondary endpoint, the nerandomilast 18 mg bid group showed significant improvements compared with placebo, including reductions in the risk of first acute ILD exacerbation or death (HR [redacted])…" "For the FIBRONEER-ILD monotherapy population, the key secondary endpoint was significant for nerandomilast than placebo". "Only time to death up to DBL2 (nerandomilast 18mg) and change from baseline in FVC % predicted at Week 52 (nerandomilast 9mg) achieved **nominal** significance in the FIBRONEER-IPF trial".	"Among the individual components of the key secondary endpoint, the nerandomilast 18 mg bid group showed **nominally** significant improvements compared with placebo, including reductions in the risk of first acute ILD exacerbation or death (HR [redacted])…" "For the FIBRONEER-ILD monotherapy population, the key secondary endpoint was **nominally** significant for nerandomilast **compared with** placebo". "Only time to death up to DBL2 (nerandomilast 18mg) and change from baseline in FVC % predicted at Week 52 (nerandomilast 9mg) achieved **nominal** significance in the FIBRONEER-IPF trial".		

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.4, Table 11, page 45.	Amend data for 'AE leading to temporary treatment interruption' row. Amend to following: DBL1: [redacted] - 18 mg BID; [redacted] – 9 mg BID and [redacted] – placebo DBL2: [redacted] - 18 mg BID; [redacted] – 9 mg BID and [redacted] – placebo	Incorrect data presented for adverse event (AE) leading to temporary treatment interruption for DBL1 and DBL2.	The EAG apologises for the incorrect values, which have now been corrected.
Section 3.2.4, Table 11, page 45.	Amend data for 'weight decreased row', DBL2, nerandomilast 18 mg BID data to align with CS. Change ([redacted]) to ([redacted])	Minor error.	The EAG cited Table 18 of the Appendix as the source of data for the proportion of weight decrease in FIBRONEER-ILD, which reports values of [redacted]. However, Table 23 of the CS reports values of [redacted]. As the values for other adverse events in Table 11 of the EAG report are taken from Tables 17 and 18 of the Appendix, which

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			are not included in the main report, we wish to retain the values reported in the Appendix for consistency.
Section 3.2.4, Table 11, page 45 and page 46.	Amend data for FIBRONEER-IPF DBL2 data for AE leading to permanent treatment discontinuation (diarrhoea): Placebo – 0 Nera 9 mg BID – 0 Nera 18 mg BID – 1 (1.1) Amend data for FIBRONEER-ILD DBL2 data for AE leading to permanent treatment discontinuation (diarrhoea): Placebo – 0 Nera 9 mg BID – 0 (0.0) Nera 18 mg BID – 3 (1.4) Data is currently CIC but should be removed as published in	Percentages of patients with diarrhoea leading to discontinuation were incorrectly reported in the Clinical Trial Report (although patient numbers were correct; correct percentages reported now).	While this is not a factual inaccuracy, we have updated the values for DBL2 as requested. We have also updated the corresponding percentages for DBL1 (n=1, 1.1% for nintedanib 18 mg BID in FIBRONEER-IPF; n=3, 1.4% for nintedanib 18 mg BID in FIBRONEER-ILD). We have also removed the confidential marking.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	DBL2 IPF and ILD publications (refer to table in Issue 10)		
Sectio 3.4.2, page 52: "The enrolment periods span over 20 years across studies, ranging from 2004–2005 (JAPICCTI-050121) to 2022–ongoing (FIBRONEER-IPF)"	Amend text in study design bullet point to: "The enrolment periods span over 20 years across studies, ranging from 2004–2005 (JAPICCTI-050121) to 2022–**2025** (FIBRONEER-IPF)"	Minor edit. FIBRONEER-IPF has been completed therefore change to be made from "ongoing" to 2025.	While the EAG notes that Table 12 of the Appendix reports the year of enrolment for FIBRONEER-IPF as 2022–ongoing, the text has been revised as requested.
Sections 4 and 5 (throughout), "FVC state", "FVC".	Amend all references to the health states to "**FVC % predicted**".	The term 'FVC state'/'FVC' is ambiguous and could be interpreted as absolute FVC, a clinical severity state, or another categorisation. In the model, health states are explicitly determined by FVC % predicted bands; stating this in full improves clarity and ensures the health-state definition is interpreted consistently with the implemented model structure.	The EAG clarifies that all instances of the use of "FVC state" and "FVC" in sections 4 and 5 refer to "FVC % predicted", as noted by the company and reflected in the economic model. All references to the health states have therefore been updated to "FVC % predicted", as requested.
Section 4.2.2, page 63: "Health states range from best FVC state (> 110%	Amend text to:	Minor edit. Health state includes patients ≥ 110%. See above comment for FVC updates.	Text has been updated as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
FVC) to the worst state (30–39.9% predicted FVC)".	"Health states range from best **FVC % predicted** state **(≥ 110% FVC % predicted**) to the worst state (30–39.9% predicted **FVC % predicted**)".		
Section 4.2.5, page 72, "The company chose the gamma curve as their preferred extrapolation for both IPF and PPF, primarily based on clinical expert validation against expectations for nerandomilast and BSC".	Amend text to: "The company chose the gamma curve as their preferred extrapolation for both IPF and PPF, primarily based on clinical expert validation against expectations for nerandomilast, **nintedanib** and BSC".	This is incomplete, as clinical expert validation also considered external plausibility against nintedanib.	Text has been updated as requested.
Section 4.2.5, page 87, Table 75: "Considers a scenario analysis, HR from NMA to maintain consistency of methodology across all active treatment comparisons: [redacted]".	Amend text to: "Considers a scenario analysis, HR from NMA to maintain consistency of methodology across all active treatment comparisons: [redacted]".	Minor edit to upper confidence interval to align with model inputs and NMA report.	Text has been updated as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.5, page 82, "apply HRs from the NMR for treatment discontinuation for NDB and NERA to be estimated from the pooled IPD data from the FIBRONEER and INPULSIS (IPF) and INBUILD (PPF)".	Amend text to: "**using** the pooled IPD data from **FIBRONEER-IPF and INPULSIS (IPF) and from FIBRONEER-ILD and INBUILD (PPF)**. "	Minor edit to clearly state the relevant trials in each population.	Text has been updated as requested.
Section 4.2.5, page 82, "A range of treatment independent curves are available (exponential, gompertz, gamma, log-logistic and log-normal)".	Amend text to: "A range of treatment independent curves are available (exponential, **Weibull**, Gompertz, gamma, log-logistic and log-normal). **Generalised gamma was tested but failed to converge for both populations**".	Weibull was also available/tested and should be included in the list, and 'Gompertz' should be consistently capitalised. In addition, generalised gamma was explored but did not converge in either population and this should be noted.	Text has been updated as requested.
Section 4.2.5, page 83, "Whilst the choice of preferred independently fitted curve are aligned, the EAG noted substantial differences between the extrapolations reported in	Statement should be removed or amended to: "**The EAG noted differences between the extrapolations reported in Appendix M of the company submission and**	The company subsequently provided an updated appendix and addendum with corrected treatment discontinuation extrapolation values aligned to those implemented in the economic model. This amendment	This is not considered a factual inaccuracy, as the issue reflected the information available at the time the EAG report was written. Although the company's addendum did

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Appendix M of the company submission and those provided within the treatment discontinuation tab of the company's economic model. The EAG suspects the difference is due to the way in which general mortality caps were provided in the model. However, as this is not the EAG's or company's preferred base case, the EAG does not consider these independently fitted curves further".	**those implemented in the treatment discontinuation tab of the economic model. The company confirmed this was a reporting inconsistency in Appendix M and submitted an addendum with corrected treatment discontinuation values aligned to the model; this correction has no impact on the cost-effectiveness results and** is not the EAG's or company's preferred base case, the EAG does not consider these independently fitted curves further".	ensures the EAG text reflects the latest submitted evidence and resolves the previously reported inconsistency.	not explicitly flag this error, the EAG acknowledges, on reflection, that updated curves were included in the appendix to the company submission addendum. As the addendum was received less than one week before the report deadline, this update was not incorporated into the EAG report. However, the EAG is happy to revise the text at this stage to acknowledge the updated treatment discontinuation curves provided in the company's addendum appendix.
Section 4.2.6, page 92: "QALYs are accrued through health state utility values (HSUVs) for %FVC state (though these are assumed equivalent in the	Amend text to: "QALYs are **calculated** using health state utility values (HSUVs) **defined by FVC % predicted health state**,".	The original phrasing is unclear and incorrectly suggests that health state utility values (HSUVs) are equivalent across each health state in the base case. In the model, utilities are different across	This is not a factual inaccuracy. In the company's base case analysis, FVC % predicted health-state occupancy is equivalent across active

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
company's base case analysis),".		each FVC % predicted health state.	treatment comparators. However, the text has been updated to clarify that this equivalence is due to the transition probabilities, rather than the HSUVs assigned to the health states.
Section 4.2.6, page 92: "Utilities for the economic model are primarily informed by IPD analysis from the pooled FIBRONEER-IPF and INPULSIS (IPF) and pooled FIBRONEER-ILD and INBUILD studies for IPF and PPF respectively".	Amend text to: "Utilities for the economic model are primarily informed by IPD analysis from the pooled FIBRONEER-IPF and INPULSIS (IPF) and **pooled FIBRONEER-ILD and INBUILD (PPF)"**.	Minor edit to clearly state the relevant trials in each population.	Not a factual inaccuracy but the text has been updated for clarity as requested.
Section 4.2.6, page 94, Table 23: "Base case: Pooled FIBRONEER-IPF & INPULSIS; Gen pop capped; adjusted for acute exacerbation history".	Amend text to: "Base case: Pooled FIBRONEER-IPF & INPULSIS; Gen pop capped, **age 70**; adjusted for acute exacerbation history".	Minor edit. Specify that HSUVs reflect utility at a given age.	Text has been updated as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6, page 95 Table 24	Reverse values in the columns: - "Base case: Pooled FIBRONEER-ILD & INBUILD; Gen pop capped; adjusted for acute exacerbation history". - "As per company base case (uncapped)". Also amend text to: "Base case: Pooled FIBRONEER-ILD & INBUILD; Gen pop capped**, age 66**; adjusted for acute exacerbation history"	Minor edit. - Specify that HSUVs reflect utility at a given age. - Numbers are reported in the incorrect columns.	The table labels have been updated to improve clarity. However, the company's approach to utility capping for PPF differs slightly from that used for IPF. The reported HSUVs for PPF were below general population norms and were therefore inflated to general population norms in the company's capped utility approach. The EAG notes that it is not straightforward to disentangle the adjustment to the underlying values from the age adjustment applied in the model but accepts that the impact on the ICER is likely to be small. The labelling of the tables has been updated, and additional explanatory text

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			has been added to pages 93 and 96 to improve clarity.
Section 4.2.6, Acute exacerbations, page 97: "They explain that there was an insufficient number of observed events in both treatment arms in FIBRONEER-IPF ([redacted] events for nerandomilast and [redacted] events for BSC) and FIBRONEER-ILD ([redacted] events for nerandomilast and [redacted] events for BSC) to estimate robust utility values".	Amend text to: "They explain that there was an insufficient number of observed events in both treatment arms in FIBRONEER-IPF ([redacted] events for nerandomilast and [redacted] events for BSC) and FIBRONEER-ILD ([redacted] events for nerandomilast and [redacted] events for BSC) to estimate robust utility values".	The values for IPF are using the 'number of acute IPF exacerbations' whereas the values for PPF are using the 'number of acute ILD exacerbations or death'. Updated so both population values are using 'number of acute exacerbation' figures only. This also aligns with Figure 13 and 14 in CS.	This is not a factual inaccuracy, as the numbers were aligned with the data provided by the company. However, the EAG report has been updated as requested to improve clarity.
Section 4.2.7, Drug acquisition costs, page 104, Table 26: "a discount of 0% were assumed for all included treatments".	Statement should be removed.	The statement that a discount of 0% was assumed is incorrect as discounted costs are provided in the table. It is clear what is undiscounted and discounted and so this note should be removed.	Text has been updated as requested.
Section 4.2.7, Liver function monitoring costs,	Amend text to:	The EAG has not provided any scenario analysis which examines	Text has been updated as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
page 105: “The EAG accepts the company’s base case assumption but provides a scenario analysis that includes a more conservative testing approach liver function test costs are applied to all active AF treatments”.	“The EAG accepts the company’s base case assumption”.	a more conservative approach on testing costs.	
Section 4.2.7, Disease monitoring costs, page 105: “The unit costs for each component included in the model were sourced from either the NHS Reference Costs 2024/25 for secondary care monitoring, or PSSRU 2024 for primary care”.	Amend text to: “The unit costs for each component included in the model were sourced from either the NHS Reference Costs 2024/25 or PSSRU 2024”.	The original statement incorrectly implies all primary care unit costs came from the Personal Social Services Research Unit (PSSRU). In the model, only some primary care contacts use PSSRU, while other community/primary care visits use NHS Reference Cost inputs	Text has been updated as requested.
Section 4.2.7, Disease monitoring costs, page 110: “A higher proportion of patients in the INBUILD Trial are European - [redacted] versus [redacted] of the no AF	Amend text to: “A higher proportion of patients in the INBUILD trial are European ([redacted] vs [redacted] of the no AF cohort in the FIBRONEER trial)”	The values reported in the original statement are incorrect. These should be updated to align with Table 17 of the CS. This should also be marked as confidential	Text has been updated as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
cohort in the FIBRONEER Trial".			
Section 4.2.7, Acute exacerbation costs, page 115: "The risks of acute exacerbation are provided in section 3 of company submission and are shown in the table below (taken from section 3.3.4 of company submission)".	Add table to document	There is no table in the EAG report as indicated by this sentence	The reference to a table summarising the risk of acute exacerbation has been removed, and a cross-reference to the relevant section of the company submission has been provided instead.
Section 5.1.2, page 126: "ICER value reported in company's addendum between nerandomilast and BSC when cute [sic] exacerbation risk is equal to that of nerandomilast varies is [redacted] , ICER value from the updated model for PPF is [redacted] ". Section 5.1.2, page 128, Table 39.	Remove statement on page 126 and update ICER in table 39	The statement misreports the ICER. The correct ICER is [redacted] per the addendum, and the acute exacerbation risk assumption does not affect the nerandomilast vs BSC ICER	The spelling of "acute exacerbation" has been corrected. The text in Table 39, scenario 7, has been updated as requested. The bullet point referring to this discrepancy has also been removed from report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.1.2, page 126: "ICER value reported in company's addendum between nerandomilast and nintedanib when cute [sic] exacerbation risk is equal to that of nerandomilast varies is [redacted], ICER value from the updated model for PPF is [redacted]". Section 5.1.2, page 128, Table 39.	Update statement on page 126 and update ICER in table 39: "ICER value reported in company's addendum between nerandomilast and nintedanib when **acute exacerbation** risk is equal to that of nerandomilast varies is [redacted] , ICER value from the updated model for PPF is [redacted]".	The statement contains an ICER value that is not reproducible from the PPF model. The addendum reports [redacted] and the model returns the same value due to a non-functional PPF scenario switch; a manual recalculation indicates the ICER should be [redacted] under the intended scenario.	This is not a factual inaccuracy. The EAG tentatively accepts the manually recalculated scenario value in the model, although it has not been able to reproduce this value. This has been noted in a footnote to Table 39. To be able to verify the company's reported ICER, the EAG would appreciate access to a version of the economic model in which all switches are fully functional. The EAG also notes that functionality to re-run deterministic scenario analyses does not readily allow scenarios to be applied to an alternative

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			configuration of the base-case assumptions. Such functionality would be welcome in the model. The spelling of “acute exacerbation” has been corrected.
Section 5.1.2, page 128, Table 39, ICER value vs NDB for scenario 7	The ICER vs NDB for scenario 7 should be [redacted].	Error as outlined in section 5.1.2, page 126. This value should be updated to [redacted].	No amendment has been made, as the value of [redacted] for Scenario 7 (Nera vs. NDB) does not align with the corrected ICER of [redacted] reported above. The EAG is unclear as to what the correct ICER is for this scenario.
Section 5.2.2, page 137, table 42, ICER value vs BSC for scenario 7	The ICER vs BSC for scenario 7 should be [redacted].	Minor edit, potential rounding error.	Text has been revised as requested.
Section 5.2.2, page 140, Figure 16	Update WTP to £25,000 or £35,000.	The willingness-to-pay line is not correct with the updated thresholds. Goes against	Sections have been revised to add WTP line at

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.2.3, page 147, Figure 18		statement made by EAG report in section 5.1 where they note that they are using updated thresholds for analysis.	£25,000 to align with updated thresholds.
Section 5.2.2, page 143, Table 43, additional scenario I Section 5.2.3, page 149, Table 45, additional scenario E "Assume 1 year of treatment for all active comparators, no treatment discontinuation".	Amend text to: "**Assume equivalence of all active treatments for transition probabilities, acute exacerbation and mortality and** assume 1 year of treatment for all active comparators, no treatment discontinuation".	Minor edit to phrasing to make clear that efficacy is the same in this scenario.	Updated as requested.

Issue 8 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Sections in the executive summary are incorrectly numbered.	Adjust numbering in the executive summary from 5.1-5.6 to 1.2-1.7.	Incorrect numbering.	The EAG apologises for the incorrect section numbering, which has now been corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.2, page 17.	Amend “Best supportive care (BSC) is routinely offered to all patients of IPF and PPF” to: “Best supportive care (BSC) is routinely offered to all patients **with** IPF **or** PPF”.	Minor edit to say IPF or PPF.	Typographical error has been corrected as requested.
EAG report page 17.	Amend ‘nelandomilast’ to ‘nerandomilast’.	Incorrect spelling of nerandomilast.	The two typographical errors have been corrected as requested.
EAG report page 77.	Amend ‘IMPULSIS’ to ‘INPULSIS’.	Incorrect spelling of trial name.	Typographical error has been corrected as requested.
EAG report page 124.	Amend ‘FINRONEER Trail’ to ‘FIBRONEER trial’.	Incorrect spelling of trial name.	Typographical error has been corrected as requested. Two additional typographical errors have been identified and corrected on page 129, where “trail” has been amended to “trial”
EAG report page 152.	Amend ‘PFN’ to ‘PPF’.	Spelling error.	Typographical error has been corrected as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 42.	Amend ‘social organ class’ to ‘system organ class’.	Incorrect statement.	Typographical error has been corrected as requested.

Issue 9 Incorrect marking of commercial-in-confidence information

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 3.2.2, HRQoL data, page 40	The following should be marked CIC: FIBRONEER-ILD (impact: [redacted] vs [redacted], symptom: [redacted] vs [redacted])	Similar results were observed in FIBRONEER-ILD (impact: [redacted], difference [redacted]; symptom: [redacted], difference [redacted]), with even smaller differences, indicating that the groups were very similar.	Confidential marking has been updated as requested
Section 4.2.5, page 88 and Table 22, page 90	The following information should not be marked CIC: one year (4 model cycles)	The company’s base case model assumes that treatment effects (for mortality and %FVC health state) are maintained for one year (4 model cycles) after the maximum duration of follow-up from the FIBRONEER trials.	Confidential marking has been updated as requested.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
		Table 22: based on 1 year post end of follow up from FIBRONEER trials	
Section 4.2.7, Disease monitoring unit costs, page 110	The following should be marked as CIC: the proportion of patients who are European in FIBRONEER-ILD and INBUILD	A higher proportion of patients in the INBUILD trial are European ([redacted] vs [redacted] of the no AF cohort in the FIBRONEER trial)* *These proportions have been updated as outlined in issue 7	Confidential marking has been updated as requested, and the numbers have been updated as per issue 7.

Issue 10 Commercial-in-confidence marking that can be removed due to publication of FIBRONEER database lock 2 results (Oldham et al. 2026[21]; Wijsenbeek et al 2026[22])

Location of CIC marking no longer needed	Description of CIC marking no longer needed	Amended marking	EAG response
Section 3.2.2, page 36 and Table 10, page 38 and page 39	Of the monotherapy cohort in FIBRONEER-IPF, the following data has now been published: The number of participants experiencing key secondary endpoint events in the nerandomilast 18 mg BID group vs. placebo (Figure 4 of	Remove marking ONLY from yellow highlighted text: In the FIBRONEER-IPF trial, among participants not taking background AF therapy (monotherapy population in the CS), key secondary endpoint up to DBL2 occurred in [redacted]	Confidential marking has been updated as requested

Location of CIC marking no longer needed	Description of CIC marking no longer needed	Amended marking	EAG response
	the FIBRONEER-IPF publication) The HR of the key secondary endpoint in the nerandomilast 18 mg BID group vs. placebo have now been published (Figure 4 of the FIBRONEER-IPF publication) The number of events and HR of time to death in the nerandomilast 18 mg BID group vs. placebo (Figure 6 of the FIBRONEER-IPF publication) The number of events and HR of time to first acute exacerbation or death up to DBL2 in the nerandomilast 18 mg BID group vs. placebo (Figure E4B in the supplementary material of the FIBRONEER-IPF publication) The number of events and HR of time to first hospitalisation	participants in the nerandomilast 18 mg bid group compared with [redacted] Although the difference did not reach statistical significance, it was considered clinically meaningful by the company, favouring the 18 mg group (HR [redacted]. Of the individual components of the key secondary endpoint, time to death was significantly improved in the nerandomilast 18 mg bid group compared with placebo (HR [redacted]). Remove marking for the following rows from Table 10 for FIBRONEER-IPF: Time to first occurrence of acute exacerbation, first hospitalisation for respiratory cause or death up to DBL2 (N with events / N analysed and HR)	

Location of CIC marking no longer needed	Description of CIC marking no longer needed	Amended marking	EAG response
	for a respiratory cause or death up to DBL2 in the nerandomilast 18 mg BID group vs. placebo (Figure E5B in the supplementary material of the FIBRONEER-IPF publication) The number of events and HR of time to death up to DBL2 in the nerandomilast 18 mg BID group vs. placebo (Figure E6B in the supplementary material of the FIBRONEER-IPF publication) The number of events and HR of time to absolute decline in FVC % predicted of >10% or death up to DBL2 in the nerandomilast 18 mg BID group vs. placebo (Figure E7B in the supplementary material of the FIBRONEER-IPF publication) The number of events and HR of time to absolute decline in	Time to first acute exacerbation or death up to DBL2 (N with events / N analysed and HR) Time to first hospitalisation for a respiratory cause or death up to DBL2 (N with events / N analysed and HR) Time to death up to DBL2 (N with events / N analysed and HR) Time to absolute decline in FVC % predicted of >10% or death up to DBL2 (N with events / N analysed and HR) Time to absolute decline in DLco % predicted of >15% or death up to DBL2 (N with events / N analysed and HR)	

Location of CIC marking no longer needed	Description of CIC marking no longer needed	Amended marking	EAG response
	FVC % predicted of >10% or death up to DBL2 in the nerandomilast 9 mg BID group vs. placebo (Figure E7A in the supplementary material of the FIBRONEER-IPF publication) The number of events and HR of time to absolute decline in DLco % predicted of >15% or death up to DBL2 in the nerandomilast 18 mg BID group vs. placebo (Figure E8B in the supplementary material of the FIBRONEER-IPF publication) The number of events and HR of time to absolute decline in DLco % predicted of >15% or death up to DBL2 in the nerandomilast 9 mg BID group vs. placebo (Figure E8A in the supplementary material of the FIBRONEER-IPF publication)		

Location of CIC marking no longer needed	Description of CIC marking no longer needed	Amended marking	EAG response
Section 2.3.3, page 36 and page 37 and Table 10, page 38 and page 39	Of the monotherapy cohort in FIBRONEER-ILD, the following data has now been published: The number of participants experiencing key secondary endpoint events in the nerandomilast 18 mg BID group vs. placebo (Figure 5 of the FIBRONEER-ILD publication) The HR of the key secondary endpoint in the nerandomilast 18 mg BID group vs. placebo have now been published (Figure 5 of the FIBRONEER-ILD publication) The HR for the reductions in the risk of first acute ILD exacerbation or death in the nerandomilast 18 mg BID group vs. placebo (Figure S11 of the FIBRONEER-ILD publication)	Remove marking ONLY from yellow highlighted text: Similarly, in the monotherapy population in FIBRONEER-ILD, key secondary endpoint events up to DBL2 were less likely to occur in the nerandomilast 18 mg bid group compared with placebo ([redacted]). Among the individual components of the key secondary endpoint, the nerandomilast 18 mg bid group showed significant improvements compared with placebo, including reductions in the risk of first acute ILD exacerbation or death ([redacted], time to first hospitalisation for respiratory cause or death ([redacted]), time to first hospitalisation for respiratory cause ([redacted]), and time to death ([redacted]).	Confidential marking has been updated as requested.

Location of CIC marking no longer needed	Description of CIC marking no longer needed	Amended marking	EAG response
	The HR for the time to first hospitalisation for respiratory cause or death in the nerandomilast 18 mg BID group vs. placebo (Figure S12 of the FIBEONEER-ILD publication) The HR for the time to death in the nerandomilast 18 mg BID group vs. placebo (Figure 7 of the FIBEONEER-ILD publication)	Remove marking for the following rows from Table 10 for FIBRONEER-ILD: Time to first occurrence of acute exacerbation, first hospitalisation for respiratory cause or death up to DBL2 (N with events / N analysed and HR) Time to first acute exacerbation or death up to DBL2 (N with events / N analysed and HR) Time to first hospitalisation for a respiratory cause or death up to DBL2 (N with events / N analysed and HR) Time to death up to DBL2 (N with events / N analysed and HR)	
Section 2.3.3, page 37	Of the monotherapy cohort, in FIBRONEER-IPF, HR for the following (in the nerandomilast 18 mg BID group vs. placebo) have now been published:	Remove marking ONLY from yellow highlighted text: At DBL2, composite endpoints in both FIBRONEER trials—time to	Confidential marking has been updated as requested.

Location of CIC marking no longer needed	Description of CIC marking no longer needed	Amended marking	EAG response
	Time to absolute decline from baseline in FVC % predicted of >10% or death (Figure E7B in the supplementary material of the FIBRONEER-IPF publication) Time to absolute decline from baseline in DLco % predicted of >15% or death (Figure E8B in the supplementary material of the FIBRONEER-IPF publication)	absolute decline from baseline in FVC % predicted of >10% or death ([redacted]) and time to absolute decline from baseline in DLco % predicted of >15% or death ([redacted]) (were numerically lower in the nerandomilast 18 mg bid group than in the placebo group.	
Section 3.2.4, page 41 and Table 11, page 44, page 45 and page 46	Data for AEs leading to treatment discontinuation in the FIBRONEER-IPF and FIBRONEER-ILD monotherapy populations has now been published (page 13 and page 12 of IPF and ILD publications, respectively)	Remove marking ONLY from yellow highlighted text: At the time of the second database lock (DBL2), the nerandomilast 18 mg bid group, compared with placebo, was associated with a lower proportion of serious AEs (FIBRONEER-IPF: [redacted] FIBRONEER-ILD: [redacted]), serious AE resulting in death (FIBRONEER-IPF: [redacted] FIBRONEER-ILD: [redacted]	Confidential marking has been updated as requested.

Location of CIC marking no longer needed	Description of CIC marking no longer needed	Amended marking	EAG response
		[redacted] AEs leading to treatment discontinuation ([redacted]), AEs leading to treatment interruption (FIBRONEER-IPF: [redacted] FIBRONEER-ILD: [redacted]), and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥3) (FIBRONEER-IPF: [redacted] FIBRONEER-ILD: [redacted] Remove marking from Table 11 for the AE leading to permanent treatment discontinuation (Any) row for FIBRONEER-IPF DBL1 and DBL2 Remove marking from Table 11 for the AE leading to permanent treatment discontinuation (diarrhoea) row for FIBRONEER-IPF and FIBRONEER-ILD DBL2 (need to correct data, refer to issue 7 for corrected data)	

Location of CIC marking no longer needed	Description of CIC marking no longer needed	Amended marking	EAG response
Section 3.2.4, page 41 and Table 11, page 44, page 45	DBL2 data for incidence of diarrhoea in the monotherapy populations of FIBRONEER-IPF and FIBRONEER-ILD have now been published (page 13 and page 12 of IPF and ILD publications, respectively)	Remove marking ONLY from yellow highlighted text: At DBL2, diarrhoea was the most frequently reported adverse event (AE) at the preferred term level across both trials, with a higher incidence in the nerandomilast 18 mg bid group than in the placebo group (FIBRONEER-IPF: [redacted] FIBRONEER-ILD: [redacted]) (Tables 17 and 18, Appendix D of Company Submission). Remove marking for the diarrhoea row from Table 11 for FIBRONEER-IPF	Confidential marking has been updated as requested.

Location of CIC marking no longer needed	Description of CIC marking no longer needed	Amended marking	EAG response
		Remove marking from the diarrhoea row from Table 11 for FIBRONEER-ILD	
Section 4.2.2, page 64, table 15	The lung transplant data for entered set (ES) in both FIBRONEER-IPF and FIBRONEER-ILD have now been published	Marking for rows “Lung transplant in ES, n (%)” in Table 15 can now be removed for both FIBRONEER-IPF and FIBRONEER-ILD	Confidential marking has been updated as requested.
Section 4.2.5, page 71	The number of events in FIBRONEER-IPF has now been published	The company justify their conclusion on the grounds that the apparent violation of the assumptions could be explained as an artefact of small event numbers in the FIBRONEER study for Nerandomilast ([redacted]) and Placebo ([redacted]).	Confidential marking has been updated as requested.

Issue 12 Additional EAG revisions to the EAG report

Description of problem	Description of amendment made to EAG report	Justification for amendment
There was an error in the automated Section numbering in the report	Section numbering has been updated.	To align with the EAG report template.
Sections 1.7 and 5.4 referred to a confidential appendix. However, given that both nerandomilast and nintedanib are Boehringer Ingelheim products, a confidential Appendix is not required.	References to a confidential appendix have been removed, and an explanation has been added to clarify that all relevant prices are included in the main EAG report.	To clarify the relevant prices of the alternative technologies.

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Appendix 1: Pooled ITC results (IPD meta-regression based on FIBRONEER-IPF, FIBRONEER-ILD, INPULSIS-1, INPULSIS-2 and INBUILD trials)

Outcome	Estimate	Unadjusted	Adjusted
Time to death over the whole trial	[redacted]	[redacted]	[redacted]
Time to first progression over the whole trial	[redacted]	[redacted]	[redacted]
Time to first acute exacerbation over the whole trial	[redacted]	[redacted]	[redacted]
Time to treatment discontinuation over the whole trial	[redacted]	[redacted]	[redacted]
CFB in FVC percent predicted at 52 weeks	[redacted]	[redacted]	[redacted]
CFB in FVC (mL) at 52 weeks	[redacted]	[redacted]	[redacted]
Time to respiratory related death over the whole trial	[redacted]	[redacted]	[redacted]
Rate of progression over the whole trial	[redacted]	[redacted]	[redacted]
Proportion of patients with progression over the whole trial	[redacted]	[redacted]	[redacted]
Proportion of patients experiencing acute exacerbation over the whole trial	[redacted]	[redacted]	[redacted]
Proportion of patients experiencing death over the whole trial	[redacted]	[redacted]	[redacted]
Proportion of patients experiencing respiratory-related death over the whole trial	[redacted]	[redacted]	[redacted]
Proportion of patients experiencing serious AE	[redacted]	[redacted]	[redacted]
Proportion of patients experiencing diarrhea over the whole trial	[redacted]	[redacted]	[redacted]
Proportion of patients experiencing GI disorders over the whole trial	[redacted]	[redacted]	[redacted]
Proportion of patients with study discontinuation	[redacted]	[redacted]	[redacted]

Proportion of patients with treatment discontinuation	[redacted]	[redacted]	[redacted]
Proportion of patients with treatment discontinuation due to AE	[redacted]	[redacted]	[redacted]
Key: AE, adverse event; CFB, change from baseline; CI, confidence interval; FVC, forced vital capacity; GI, gastrointestinal; HR, hazard ratio; MD, mean difference; OR, odds ratio; RR, rate ratio.			

Appendix 2: FIBRONEER trials – premature discontinuation data

Table 1: Premature trial treatment discontinuation in FIBRONEER-IPF for the monotherapy population

	Nera 18 mg bid N = 87	**Nera 9 mg bid N = 88**	**Placebo N = 87**	**Total N = 262**
Prematurely discontinued treatment before DBL2	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Source: FIBRONEER-IPF CTR (Table 10:5).[6]				

Table 2: Premature trial treatment discontinuation in FIBRONEER-ILD for the monotherapy population

	Nera 18 mg bid N = 220	**Nera 9 mg bid N = 220**	**Placebo N = 222**	**Total N = 662**
Prematurely discontinued treatment over the while trial	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by patient	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Source: FIBRONEER-ILD CSAP-228 (Table 69.1.1.1).[7]				

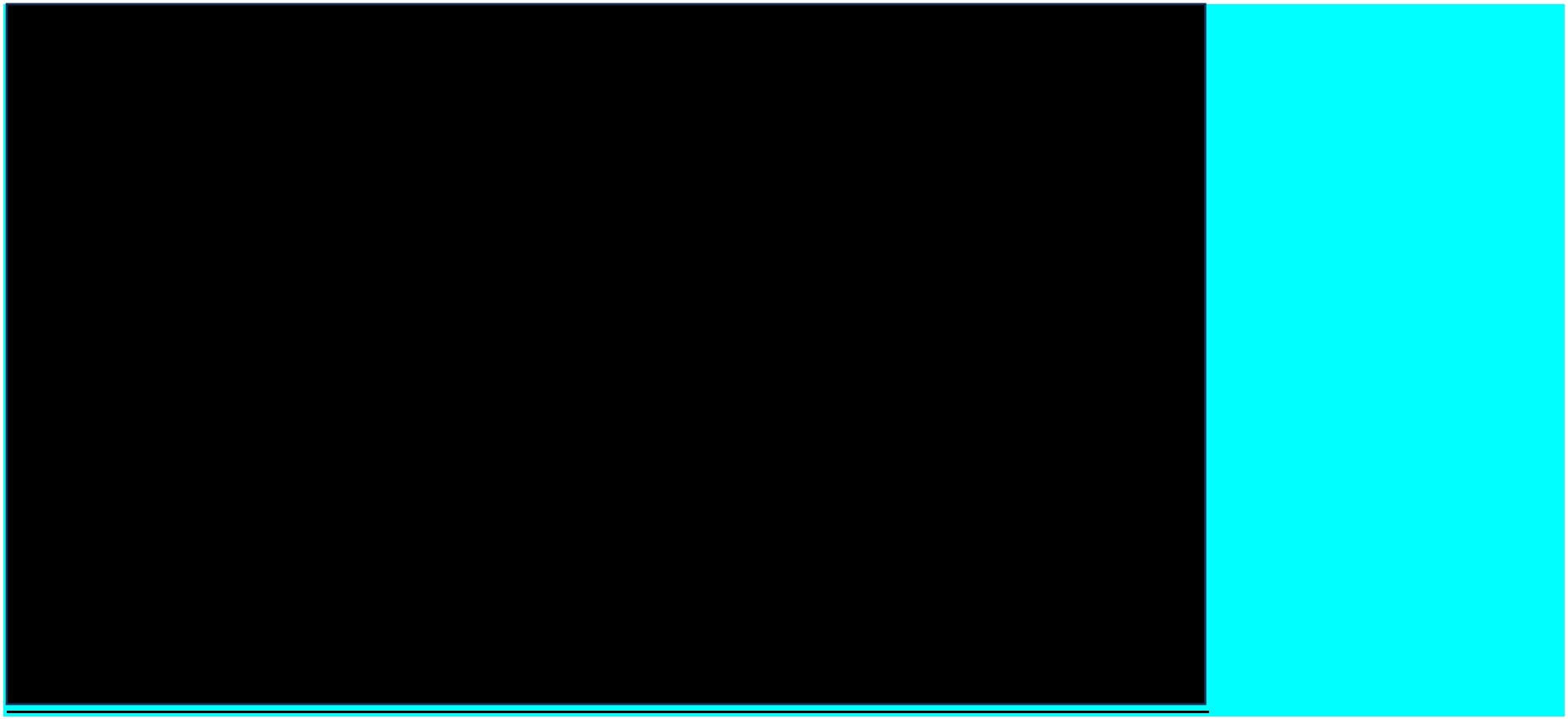
Appendix 3: Figures supporting company's waning assumptions



Figure 4. Long-term OS extrapolations with different treatment waning assumptions - IPF

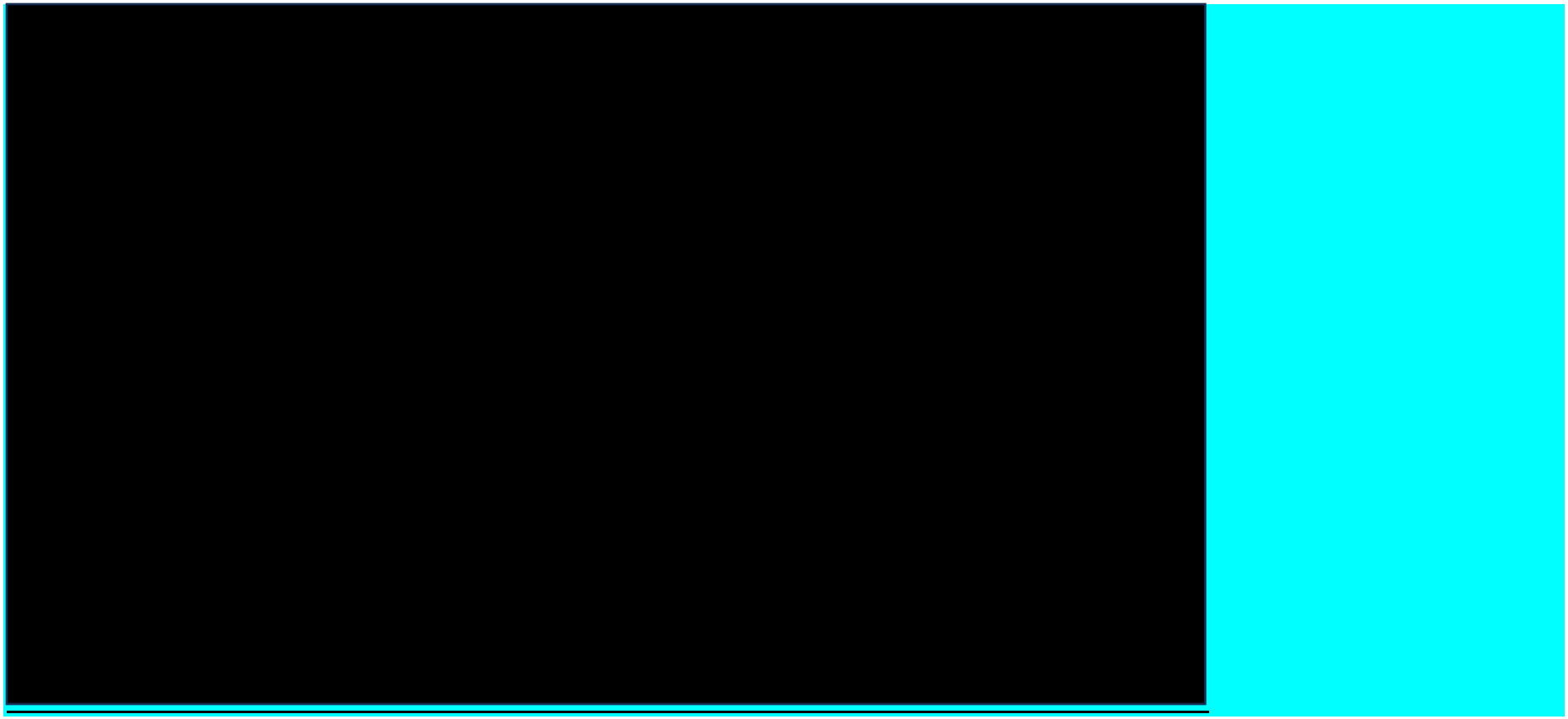
Key: IPF, idiopathic pulmonary fibrosis, OS, overall survival, SEE, structured expert elicitation.

Figure 5. Long-term OS extrapolations with different treatment waning assumptions - PPF



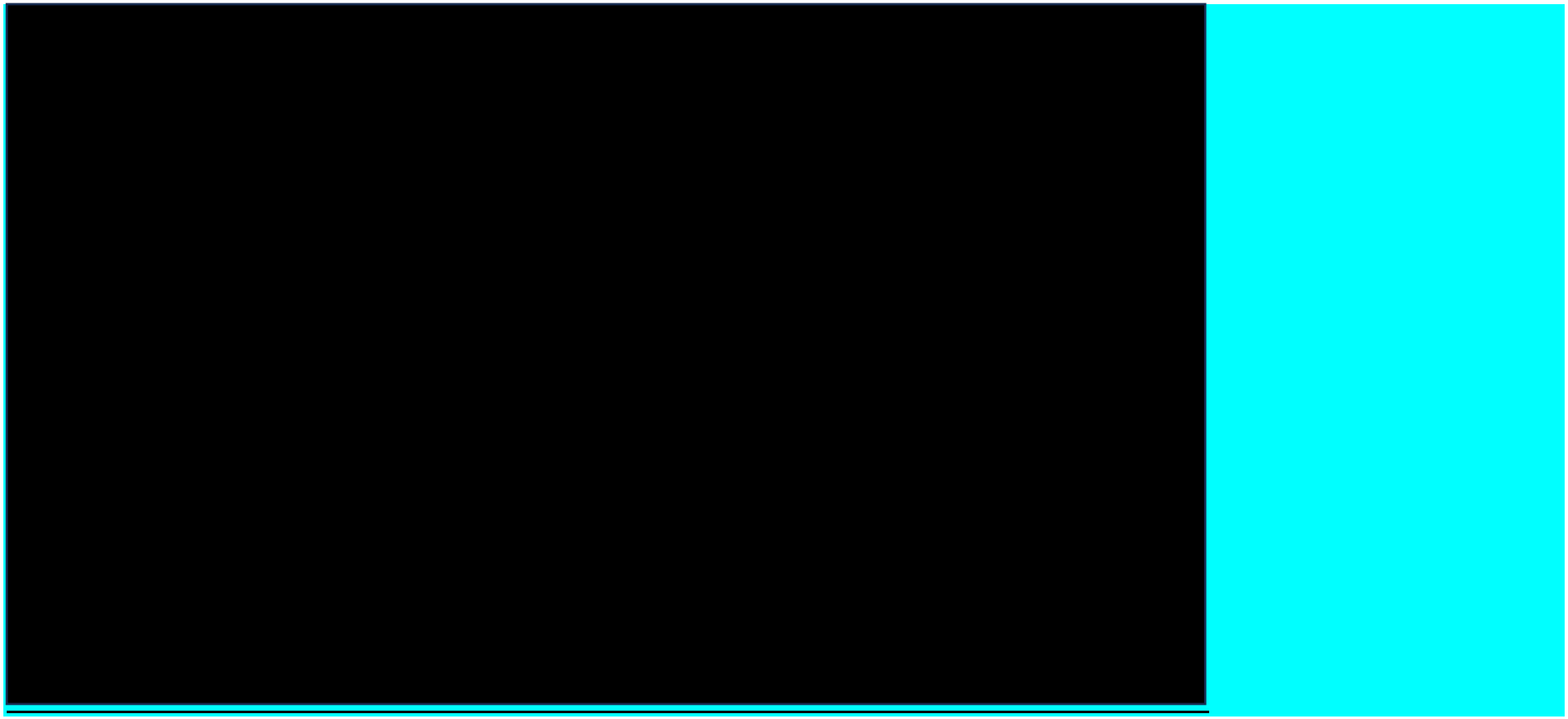
Key: OS, overall survival, PPF, progressive pulmonary fibrosis; SEE, structured expert elicitation.

Figure 6. OS hazards under modelled waning assumptions - IPF



Key: BSC, best supportive care; IPF, idiopathic pulmonary fibrosis; NDB, nintedanib; Nera, nerandomilast; OS, overall survival.

Figure 7. OS hazards under modelled waning assumptions - PPF



Key: BSC, best supportive care; NDB, nintedanib; Nera, nerandomilast; OS, overall survival; PPF, progressive pulmonary fibrosis.

Appendix 4: Outcomes of published NMAs (nerandomilast not included in the network)

Table 3. Outcomes of published NMAs (nerandomilast not included in the network)

Outcome	Comparison	Canestaro, 2016[23]	Fleetwood, 2017[24]	Pitre, 2022[25]	Rinciog, 2017[26]	Rochwerg, 2016[27]	Skandamis, 2019[28]
Decline ≥10 percentage points in FVCpp	NDB vs PBO	OR: 0.57 (0.20, 1.29)	OR: 0.65 (0.42, 1.02)	-	OR: 0.54 (0.42, 0.69)	-	OR: 0.59 (0.41, 0.84)
	PFN vs PBO	OR: 0.50 (0.21, 1.04)	OR: 0.58 (0.40, 0.88)	-	OR: 0.55 (0.41, 0.72)	-	OR: 0.54 (0.37, 0.80)
	NDB vs PFN	OR: 1.14 (0.83, 1.67)	OR: 1.11 (0.60, 2.00)	-	OR: 0.98 (0.67, 1.42)	-	OR: 1.10 (0.49, 2.22)
Change from baseline in FVCpp	NDB vs PBO	-	MD: 3.2 (2.0, 4.4)	MD: 2.92 (1.51, 4.14)	-	-	-
	PFN vs PBO	-	MD: 3.4 (1.9, 4.9)	MD: 2.47 (-0.08, 5.01)	-	-	-
	NDB vs PFN	-	MD: -0.2 (-2.1, 1.7)	MD: 0.43 (-2.44, 3.24)	-	-	-
Change from baseline in absolute FVC	NDB vs PBO	-	MD: 110 (0, 220)	MD: 120 (-6, 260)	-	-	-
	PFN vs PBO	-	MD: 0.12 (0.03, 0.21)	MD: 130 (-28, 280)	-	-	-
	NDB vs PFN	-	MD: -10 (-150, 130)	MD: -8 (-140, 140)	-	-	-
Acute exacerbation	NDB vs PBO	-	-	-	OR: 0.56 (0.35, 0.89)	-	OR: 0.61 (0.20, 1.90)
	PFN vs PBO	-	-	-	OR: 1.10 (0.43, 2.85)	-	OR: 0.77 (0.26, 2.28)
	NDB vs PFN	-	-	-	OR: 0.51 (0.18, 1.46)	-	OR: 2.56 (0.06, 100)
Time to acute exacerbation	NDB vs PBO	-	-	-	-	-	-
	PFN vs PBO	-	-	-	-	-	-

Outcome	Comparison	Canestaro, 2016[23]	Fleetwood, 2017[24]	Pitre, 2022[25]	Rinciog, 2017[26]	Rochwerg, 2016[27]	Skandamis, 2019[28]
	NDB vs PFN	-	-	-	-	-	-
Death	NDB vs PBO	OR: 0.71 (0.13, 3.82)	-	RR: 0.69 (0.44, 1.10)	OR: 0.70 (0.45, 1.09)	OR: 0.68 (0.35, 1.36)	OR: 0.70 (0.45, 1.09)
	PFN vs PBO	OR: 0.65 (0.15, 2.75)	-	RR: 0.70 (0.47, 1.42)	OR: 0.69 (0.45, 1.04)	OR: 0.65 (0.33, 1.13)	OR: 0.68 (0.46, 1.03)
	NDB vs PFN	OR: 1.10 (0.12, 10.00)	-	RR: 0.86 (0.42, 1.75)	OR: 1.02 (0.55, 1.87)	OR: 1.05 (0.45, 2.78)	OR: 1.08 (0.52, 2.63)
Respiratory-related Death	NDB vs PBO	OR: 0.44 (0.05, 3.16)	-	-	-	-	-
	PFN vs PBO	OR: 0.51 (0.06, 3.76)	-	-	-	-	-
	NDB vs PFN	OR: 1.15 (0.06, 25.00)	-	-	-	-	-
Time to death	NDB vs PBO	-	OR: 0.70 (0.32, 1.55)	-	-	-	-
	PFN vs PBO	-	OR: 0.52 (0.28, 0.92)	-	-	-	-
	NDB vs PFN	-	HR: 1.35 (0.51, 3.70)	-	-	-	-
Serious adverse events	NDB vs PBO	-	-	RR: 0.98 (0.83, 1.16)	-	OR: 0.96 (0.55, 1.56)	OR: 0.99 (0.78, 1.28)
	PFN vs PBO	-	-	RR: 0.95 (0.76, 1.19)	-	OR: 1.00 (0.59, 1.66)	OR: 1.00 (0.78, 1.29)
	NDB vs PFN	-	-	RR: 1.03 (0.78, 1.36)	-	OR: 0.96 (0.45, 1.96)	OR: 0.98 (0.62, 1.61)
Study discontinuations	NDB vs PBO	-	-	-	OR: 1.42 (1.08, 1.87)	-	OR: 1.61 (1.13, 2.28)
	PFN vs PBO	-	-	-	OR: 1.34 (1.34, 1.73)	-	OR: 1.27 (0.96, 1.68)
	NDB vs PFN	-	-	-	OR: 1.06 (0.73, 1.54)	-	OR: 1.33 (0.79, 3.03)

Outcome	Comparison	Canestaro, 2016[23]	Fleetwood, 2017[24]	Pitre, 2022[25]	Rinciog, 2017[26]	Rochwerg, 2016[27]	Skandamis, 2019[28]
Treatment discontinuations	NDB vs PBO	-	-	-	-	-	-
	PFN vs PBO	-	-	-	-	-	-
	NDB vs PFN	-	-	-	-	-	-
Treatment discontinuations due to AE	NDB vs PBO	-	-	RR: 1.45 (1.05, 2.02)	-	-	-
	PFN vs PBO	-	-	RR: 1.72 (1.16, 2.75)	-	-	-
	NDB vs PFN	-	-	RR: 0.84 (0.48, 1.39)	-	-	-

Key: FVCpp, percentage of predicted forced vital capacity; MD, mean difference; NDB, nintedanib; NMA, network meta-analysis; OR, odds ratio; PBO, placebo; PNF, pirfenidone; RR, relative risks.

NICE National Institute for Health and Care Excellence®

Additional Questions to Clinical Experts

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis [ID6446]

The following questions were asked of the Clinical Experts by the NICE Technical Team:

Based on your experience of NHS clinical practice, please provide your views on the management of idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF).

Where possible, for each response, please indicate your level of confidence using the following scale:

- High – reflects established or consistent NHS practice and/or is supported by evidence.
- Moderate – reflects common practice or informed clinical judgement, although practice may vary between centres.
- Low – reflects personal opinion or an area where there is substantial uncertainty or variation in practice.

Where your responses reflect variation in practice across NHS centres, please indicate the extent of this variation and whether you expect practice to become more standardised in the future.

1. Continued clinical benefit after treatment discontinuation

Following discontinuation of antifibrotic treatment, would you expect patients to continue to derive any clinical benefit attributable to the treatment? Please explain your answer and, if yes, indicate:

- Approximately how long you would expect this benefit to last.

- Whether clinical benefit depends on the reason for treatment discontinuation (e.g. adverse events, disease progression or patient choice).

Response from Dr Sophie Fletcher
Following discontinuation of the treatment, the potential benefits of the treatment cease.
Response from Professor Philip Molyneaux
On discontinuation I would not expect any sustained benefit. Registry data suggest that patients who discontinue an antifibrotic have significantly worse outcomes compared to those whom continue or switch to another drug. This has been seen in multiple observational datasets including the EMPIRE registry (PMID: 38160169). (High based on evidence)

2. Waning of treatment effect whilst on treatment

While patients remain on antifibrotic treatment, do you consider treatment effectiveness to remain broadly constant throughout treatment, or to wane over time?

If you consider treatment benefit to wane while patients remain on treatment, please indicate:

- Approximately when you would expect waning to begin.
- Whether you would expect waning to occur gradually or abruptly.

Response from Dr Sophie Fletcher
If the patient remains on a steady dose of the anti fibrotic treatment the benefit will remain consistent. This is evidence by the pharmacokinetics of the drug and the continued efficacy of the treatment over time as evidenced in the trial data.
Response from Professor Philip Molyneaux
There is no evidence for waning of antifibrotic effect over time. Long term real-world data from Lalla et al. (BMC Pulm Med, 2025) showed sustained FVC decline attenuation with both nintedanib and pirfenidone in almost 300 patients over 5 years, with no evidence of waning efficacy. The additional data out to 76 weeks in the Fibroneer study, continue to show clear separation of the FVC curves between treated and non treated patients, again supporting no waning effect. (High based on evidence)

3. Stopping rules

- In current UK clinical practice, what are the main reasons for stopping antifibrotic treatment?

- Are decisions about stopping antifibrotic treatment made differently in patients with PPF compared with IPF? If so, please describe the differences.

- Is an absolute decline in FVC % predicted of more than 10% generally used as a stopping criterion? If not, how is treatment failure typically assessed, and what factors are considered when deciding whether to continue or stop treatment?

- Overall, to what extent does the company's assumption that treatment is stopped immediately following an FVC % predicted decline of more than 10% reflect routine NHS clinical practice? Please explain your answer, including any circumstances in which treatment might be continued despite disease progression.

Response from Dr Sophie Fletcher

- In current UK clinical practice, what are the main reasons for stopping antifibrotic treatment?

The patient entered a palliative phase of the disease where quality of life is paramount and avoidance of side-effects that impair quality of life attributable to treatment dictates cessation of treatment

- Are decisions about stopping antifibrotic treatment made differently in patients with PPF compared with IPF? If so, please describe the differences.

The clinical decision-making is the same for both groups

- Is an absolute decline in FVC % predicted of more than 10% generally used as a stopping criterion?

There is a stopping criteria for the use of nintedanib or Pirfenidone in the context of idiopathic pulmonary fibrosis as outlined in TA 504 and TA 379

- If not, how is treatment failure typically assessed, and what factors are considered when deciding whether to continue or stop treatment?

Patient preference, patient tolerance of treatment, side-effect burden, Re prioritisation of factors that influence quality of life as the palliative phase is approached

- Overall, to what extent does the company's assumption that treatment is stopped immediately following an FVC % predicted decline of more than 10% reflect routine NHS clinical practice? Please explain your answer, including any circumstances in which treatment might be continued despite disease progression.

If the forced vital capacity has reduced by more than 10% in 12 months despite being on treatment this is suggestive of an aggressive form of fibrotic lung disease, rather than the drug has failed. This significant rate of decline often prompts a clinical conversation that will include the rationale for continuation of anti fibrotic. The outcome of the discussion will depend upon patient preference alongside how advanced their fibrotic lung disease is. It is not an automatic immediate to discontinuation as evidence from experience with patients with progressive pulmonary fibrosis who offered nintedanib where there is no such stopping rule.

Response from Professor Philip Molyneaux

In the UK the main reason for discontinuation of antifibrotic therapy is intolerance. There are no differences in decision making between IPF and PPF.

An absolute deline in FVC of 10% is associated with subsequent mortality and is therefore associated with a negative outcome. However, clinically we appreciate that without antifibrotic drugs this decline would have been worse, so therefore this is not seen as a treatment failure (as we cannot know what would have happened without the drug). In my experience most clinicians would rather continue a well tolerated drug when a patient declines than switch to another where side effects could be an issue.

Under current NICE guidance antifibrtoic drugs should be stopped as soon as there is progression (defined as FVC declines by 10% or greater during a 12 month period). Therefore this assumption is reasonable. Though in practice, application of this rule varies across centres, and many clinicians exercise clinical judgement rather than applying the stopping rule rigidly, particularly in patients who are otherwise tolerating treatment well

(Moderate - clinical practice and informed clinical judgement)

4. Treatment sequencing

The company's economic model assumes that patients receive only 1 active antifibrotic treatment and do not switch to a second active treatment following discontinuation or loss of treatment effectiveness.

- Would you expect clinicians to prescribe antifibrotic treatments sequentially if more than 1 treatment were routinely available for the same indication? Please describe how you would expect treatments to be used in NHS clinical practice, including whether your views differ for IPF and PPF.

- What would be the main reasons for switching from 1 antifibrotic treatment to another? For example, would switching most commonly occur because of adverse events or intolerance, lack or loss of effectiveness, disease progression, patient preference or other factors?

- If patients switched from 1 antifibrotic treatment to another, would you expect them to derive meaningful additional clinical benefit? Would your answer differ depending on whether the first treatment was stopped because of intolerance or because of disease progression?

- Approximately what proportion of patients would you expect to receive:
    - only 1 antifibrotic treatment;
    - 2 sequential antifibrotic treatments; or
    - more than 2 active antifibrotic treatments?

Response from Dr Sophie Fletcher

- Would you expect clinicians to prescribe antifibrotic treatments sequentially if more than 1 treatment were routinely available for the same indication? Please describe how you would expect treatments to be used in NHS clinical practice, including whether your views differ for IPF and PPF.

I would expect clinicians to offer anti fibrotic treatments sequentially as patient's differ in their tolerance to these medications and their other medications may change which influence the risk profile of the anti fibrotic choice.

- What would be the main reasons for switching from 1 antifibrotic treatment to another? For example, would switching most commonly occur because of adverse events or intolerance, lack or loss of effectiveness, disease progression, patient preference or other factors?

I suspect the initial choice will be made based on patients preference to potential side-effects, there will be an influence dependent on drug availability and patient other medications for example, nintedanib may be avoided if the patient is anticoagulated.

- If patients switched from 1 antifibrotic treatment to another, would you expect them to derive meaningful additional clinical benefit?

Yes and I have done this

- Would your answer differ depending on whether the first treatment was stopped because of intolerance or because of disease progression?

I have only ever change from 1 treatment to another because of intolerance, this is done in frequently but often results in the 2nd agent also being poorly tolerated. I have not changed from 1 treatment to another because of perceived lack of efficacy because the evidence for both current medications in terms of efficacy are similar, this is borne out by real world clinical experience.

- Approximately what proportion of patients would you expect to receive:

Of those eligible and were anti fibrotic medication is indicated

  - only 1 antifibrotic treatment

80%

  - 2 sequential antifibrotic treatments;

10%

  - Or, more than 2 active antifibrotic treatments?

10%

Response from Professor Philip Molyneaux

My views do not differ on any answer for IPF or PPF.

I would expect clinicians to prescribe the drug they feel will be best tolerated and have the most chance of efficacy. Where multiple drugs

are deemed to be as efficacious then the choice would come down to tolerability, based on side effects. While current antifibrotic agents have been shown to slow FVC decline they are poorly tolerated in the real wold and therefore patients are not getting the longer term mortality benefits we would hope for.

If someone were to deteriorate on therapy I would expect a clinician to either add in an additional therapy, where the original drug is well tolerated or switch to another drug if the original drug is poorly tolerated. The main reason for switching would be intolerance due to side effects.

If patient switched and were then on a drug they were able to tolerate I would expect them to gain benefit over being on a drug where they were not achieving target dose, missing doses regularly and not being able to tolerate long term. If a patient were to decline on one therapy the addition of a second agent would hopefully allow them to derive benefit. In addition choosing a drug with a differing mechanism of action may also allow potential benefit following a deterioration.

I would not expect any patients to be on three agents in the UK as nintedanib and pirfenidone are not prescribed together due to the significant side effect burden. I would expect the majority of patients to be on single therapy (50%), 20% on two active therapies (given the poor tolerance of both nintedanib and pirfenidone and then 30% to be on sequential therapy. (Medium to low).